Responses to Major Comments on Technical Support Document

Public Health Goal
For
Arsenic
In Drinking Water

Prepared by

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INTRODUCTION

The following are the combined 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 arsenic, based on the various review drafts. These comments have been carefully considered, and changes in the PHG document have been made in response to them. 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.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from U.C. Peer Reviewer #1

Comment 1. "…there should be conclusions in the health endpoint sections. That is, in addition to the focus on carcinogenicity, which is the primary endpoint of concern and the endpoints used for benchmark dose calculations there should be conclusions drawn on other endpoints. For example, the section on human neurotoxicity reviews a number of studies but there is no conclusion drawn about arsenic and neurotoxicity."

Response 1. Conclusions have been added to several toxicology subsections. With regard to neurotoxicity, none of the studies reviewed was judged suitable for quantitative risk assessment. A study on developmental neurotoxicity in children cited in the human developmental and reproductive toxicology section has now been added to the studies subjected to quantitative analysis.

Comment 2. "The document is not consistent in its nomenclature. … the terms like arsenite, arsenate, MMA, DMA, etc. should be defined, e.g., arsenite (As III) and then As III should be used from that point on."

Response 2. A list of common abbreviations for the arsenic species used in the document is provided in the footnote to the Introduction.

Comment 3. " In my view the sections on production and uses and environmental occurrence and exposure require improvement. … The document should describe the uses in California; there are no copper smelters here so that fact is not relevant. The document does not address pesticidal uses in the State.…"

Response 3. OEHHA thinks that the exposure information provided in the document is adequate considering the scope and purpose of the document, which is to develop a public health goal for arsenic in drinking water. The primary exposure route and source of concern is ingestion of inorganic arsenic in drinking water. The latest surveys of arsenic in water have been cited in the document. The Department of Health Services, which will manage arsenic risks in drinking water through the establishment of a maximum contaminant level (MCL), is continuously monitoring drinking water contaminants, including arsenic.

Comment 4. " The section on 'Developmental and Reproductive Toxicity' contained a review of a large number of articles, but in the end there were no overall conclusions drawn. It is not clear what the reader is to take from the lengthy review and the conclusion that does exist seems incomplete."

Response 4. OEHHA thinks our overall conclusion, namely that based on animal studies reviewed **"**it would appear unlikely that environmental levels of arsenic exposure would be sufficient to cause any developmental or reproductive effects in exposed humans" is adequate. We also note in this conclusion that some human epidemiological studies have indicated potential for adverse effects and these are discussed in the section on human DART effects. It is also noted here and elsewhere in the document that experimental animals are generally less sensitive to the toxic effects of arsenic and that caution needs to be exercised in extrapolating animal data to human risks.

Comment 5. "Since there is some evidence for a role of oxidative stress in carcinogenesis, the studies on immunotoxicity are possibly relevant but there is no analysis of possible links between animal and human studies of immunotoxicity and carcinogenesis. The discussion of immunotoxicity is a review but the relevance to various health outcomes is unclear."

Response 5. At present it is uncertain what effect arsenic induced immunotoxicity may have on other arsenic endpoints, specifically cancer. Here and elsewhere in the document descriptive material was included as part of our review of relevant literature irrespective of its ultimate use in the quantitative risk assessment. See response to comment 1.

Comment 6. "The section on 'Mode of Action' … lacks a context. It is not apparent to this reviewer why the particular articles were selected or what is their relevance although they may have some implications for cardiovascular effects."

Response 6. The section on Dose Response Assessment is divided into non-cancer and cancer subsections. Each of the subsections discusses mode of action which is relevant to low dose extrapolation for carcinogens and possibly for certain noncarcinogens. The studies covered in this section (animal and human) are those that were selected for dose-response analysis.

Comment 7. "The animal studies section appears incomplete and the discussion of some of the studies seems inadequate. Papers or perhaps reports by Michael Waalkes on animal carcinogenicity are missing. The section on DNA methylation as a mechanism of action should include our recent work on the effects of nutritional changes in DNA methylation and the literature review on methylation could be updated."

Response 7. The work of Waalkes *et al*. on the transplacental cancer assay of arsenite in mice is now included although it is only available in abstract. The work on methyl-deficient diets and genomic changes in arsenic treated mice is now also cited and discussed.

Comments from U.C. Peer Reviewer #2

Comment 1. "Of major concern were some internal inconsistencies with regard to the evidence by Yamamoto (1995). In light of a previous lack of confirmation of carcinogenicity of inorganic arsenic in whole animal studies, this study appears to be a critical link, in that it shows unequivocal cancer promoting activity in animals administered DMA."

Response 1. The discussion of the promoting and carcinogenicity of arsenic metabolites has been expanded. The studies of DMA-induced carcinogenicity following carcinogen pretreatment are difficult to interpret with respect to human risk largely due to the high doses required to produce an effect and the complexity of the experimental protocols used. Also, there are significant differences in metabolism of arsenic in the rat versus the human. Rats store arsenic in red blood cells unlike humans and the extent of methylation and dimethylation vary. The findings of Wei *et al.* (1999, 2002) of direct carcinogenicity of DMA in rat urinary bladder appear to confirm the pretreatment studies although the doses required to produce an effect are still very high (50 ppm DMA for 97 weeks).

Comment 2. "The approach to derivation of the PHG is somewhat deficient. The higher standard of safety for carcinogenicity as compared with cardiovascular and endocrinologic damage does not seem to be justified nor does it appear to be consistent with the mandate. The rationale for use of a $1/10^6$ risk for cancer vs. a $1/10^2$ or $1/10^4$ risk for cerebrovascular disease mortality is not provided, and it is not clear if there is a basis for it."

Response 2. The comment is essentially correct. The difference in risk standard is based on current and historic risk assessment practice at the state and federal levels. In general, carcinogens with unknown or genotoxic modes of action are subjected to low-dose extrapolation to a negligible lifetime theoretical risk of $1x10^{-6}$. Carcinogens with nonlinear modes of action and noncarcinogens are not extrapolated to $1x10^{-6}$ but other margins of exposure are applied to their appropriate NOAELs, LOAELs, etc., depending on the available data. The supporting rationale is that genotoxic carcinogens are more likely to exhibit linearity of dose response to very low risk levels (a single molecule potentially initiating carcinogenesis), whereas nonlinear carcinogens and noncarcinogens are more likely to exhibit a threshold (doses below which there is little or no probability of an adverse effect). This is an area where risk assessment practices are under continuous reevaluation.

Comment 3. "The quantal model for vascular and other endpoints appears to produce results that are incompatible with the empirical data. The estimates for safe doses, even assuming that a 1% excess risk is acceptable, are far higher than would be concluded using the observed LOAELs for cerebrovascular disease and cerebral infarcts."

Response 3. OEHHA does not agree with the comment. The point is that there are no LOAELs in these studies but rather estimated exposure ranges and assigned midpoints. The benchmark dose response approach (BMR) uses all the available data to calculate the lower bound on a (statistically) suitable response level, in this case the 95 percent lower

bound on the 1 percent response. This is not the safe level but can be compared to a LOAEL to which we provide a margin of exposure via typical uncertainty factors (UFs) and an allowance for other sources of exposure, in this case totaling 150-fold. Whether the margins of exposure we applied are sufficient for the respective disease endpoints is a valid point of comment. OEHHA staff members have discussed these issues at length and concluded that the UF is adequate in this case.

Comment 4. "Face validity: … Specifically what proportion of lung and bladder cancer deaths in California are likely to be attributable to arsenic in drinking water at current levels?"

Response 4. The document does not contain a detailed exposure assessment. However, information from surveys cited in the document can be used to estimate a mean arsenic concentration in drinking water of about 3.1 μg/L (assuming 50:50 ground water:surface water use). This is a system-based average not a population-based average. Using the potency from the document a lifetime theoretical cancer risk estimate can be calculated as follows: 2.7×10^{-4}/μg/L x 3.1 μg/L = 8.4×10^{-4}. From the document, the annual deaths from lung and bladder cancer in California in 1996 were 13,600 and 1,050, respectively. Assuming 30 million exposed to community drinking water systems this translates to a 4.9×10^{-4} annual risk or a 3.4 percent lifetime risk. Thus the estimated lung and bladder cancer risk attributable to arsenic is relatively small, 0.084/3.4 = 2.5 percent. This seems a reasonable estimate since there are other well-known risks contributing to the overall mortality values.

Comment 5. "A better explanation is needed with regard to the range of exposure for the study by Siripitayakunkit , as 0.48 to 26.94 μg/g hair seems rather wide (50-fold). Can this paper be used for a neurodevelopmental quantitative assessment?"

Response 5. We have expanded the description of this study and subjected it to a quantitative analysis using a continuous BMR approach. The study suffers from relatively low numbers in the low exposure group and the indirect exposure measure of hair arsenic rather than drinking water arsenic. Nevertheless, the projected health protective water concentration is similar to the other noncancer endpoints analyzed.

Comment 6. [Referring to the human non-cancer section] "Generally this section needs some structure and organization. … The document should make clear the distinction between mortality and morbidity and the implications in interpretation of studies. For instance diabetes mortality studies are likely to underestimate the considerably larger burden of disease from living with this condition. This section should cite Tsai *et al*. (1995); those data provide information that is useful for comparing the relative impact on cancers vs. other causes of death."

Response 6. The section has been revised as suggested with separate subsections for diabetes and skin effects and a new overview of the non-cancer epidemiology including the comparative risk data of Tsai *et al*. (1995).

Comment 7. "The description of Hopenhayn-Rich *et al*. is a bit misleading. Declines in fetal and infant mortality were observed in just about every country in the world over the time period studied. As written, the document implies that this decline was particularly noteworthy and/or that it obscured or negated the effects of arsenic."

Response 7. The description of this study has been clarified.

Comment 8. "The empirical numbers in this section are not consistent with the values interpreted as LOAEL's from the fitting of a 'quantal linear model'. While the document argues strongly for transparency, concentrations of 25 μg/L (the midpoint of the 2nd category used in Chiou *et al*.) are associated with a 1.4% increase (focusing on the models that are adjusted for age, sex,, smoking, and alcohol) in the risk of cerebrovascular disease. Similarly using the cumulative dose, a 1.1% increased risk is seen for 2.5 mg/L years. The fact that the quantal linear regression results in an ED01 of 274 μg/L and 4.8 mg/L-yrs. Values that are 12 and 2 times higher that the empirical results, suggests either some error in the calculations or interpretation, or an inappropriate model (grossly inappropriate for the μg/L dose)."

Response 8. OEHHA does not agree with the comment. The study of Chiou *et al.* (1997) defines a dose-response rather than a LOAEL for cerebrovascular effects (CVD and CI). The exposure categories range from <0.1 ppb to ≥300 ppb inorganic arsenic for a response of about one to three percent. Our BMR analysis, which used all the data with the midpoints of the exposure categories, gave adjusted ED01 values of 274-293 and 233-245 ppb for CVD and CI, respectively, and LED01 values of 156-164 and 149-155 ppb. Only the adjusted CI values had an adequate model fit. With the cumulative dose estimates adjusted LED01s for CVD were 2.5-2.8 mg/L yr and for CI 3.2-3.6 mg/L yr. Only the 2.5 value for CVD (age, sex adjusted) didn't give an adequate model fit. The LED01 or benchmark dose is not the safe level but is treated as a LOAEL in our analysis with an overall margin of exposure of 150 (uncertainty factors and relative source contribution) to estimate a health-protective concentration. OEHHA does not think that the second exposure category (0.1 to 50 μg/L) represents a LOAEL but rather a "point" on a dose-response relation.

Comment 9. "Given the extremely tight confidence intervals in the data from Chiou *et al.*, in which p-values for individual data points were <0.01 and <0.001 and the p-values for goodness of fit (0.03 and 0.05), there appears to be no doubt that the model used fits poorly. While a better fitting model could be proposed, a biologic rationale might be difficult to develop. This situation argues for use of the empirical LOAEL, which can be seen directly in the published data."

Response 9. A better fitting model might be found, and the models used in BMR analysis have no biological significance but are curve-fitting tools. OEHHA does not believe that the midpoint of the second exposure category, 25 μg/L, represents an empirical LOAEL (EL). However, if we were to take that approach, the noncancer health-protective values would be several-fold lower.

For example:

Using the EL approach: $C = \frac{25\ \mu g/L \times 0.2\ RSC}{30\ UF} = 0.17\ \mu g/L$

Using the BMR approach: $C = \frac{166\ \mu g/L \times 0.2\ RSC}{30\ UF} = 1.1\ \mu g/L$

We think that the vascular effects, diabetes, and the skin effects show a similar linear or slightly curvilinear dose responses and that these are best analyzed using as much of the data as possible with a BMR approach. The degrees of model fit vary but most exceed P = 0.1 and all exceed P = 0.05 by X^2 goodness of fit test. This meets or exceeds current U.S. EPA guidance on BMR analysis. Whether or not we have applied a sufficiently protective margin of exposure for the individual noncancer endpoints is a valid point of inquiry. In the examples above, we used an uncertainty factor of 3 for LOAEL to NOAEL, 3 for interindividual variability, and 3 for severity of effect, plus a 20 percent (default) relative source contribution.

Comment 10. "The findings of Yamamoto are highly relevant to the mode of action, vis-à-vis tumor-promoting activity. These results must be incorporated into any discussion of the carcinogenic mode of action of arsenic. This section discusses sublinearity under the assumption that 'inorganic arsenic is the main carcinogenic agent' - in spite of current understanding, based on strong evidence that it is not."

Response 10. The reviewer has apparently concluded based on the studies of Yamamoto and others that DMA is the sole ultimate carcinogen resulting from inorganic arsenic exposure. OEHHA thinks that the current level of evidence is insufficient to establish a sole mode of action and ultimate carcinogen, if one exists. Rather we think it is more likely that several arsenic species may be involved in various MOAs in different target tissues. As noted elsewhere in these responses we have expanded our discussion of DMA carcinogenicity.

Comment 11. "The statement is made that smoking rates are now falling over time. References should be supplied. Sometime over the last decade, smoking rates were falling for men, but rising for women. The female trend may have reversed in California. In any case, the document should clarify any statements about what is happening with smoking rates by specifying what geographic area and what year the data cover, as well as the source of the data. The State of California collects the relevant data, that should be cited here."

Response 11. A parenthetical internet citation to the California Department of Health Services documentation of recent adult and youth smoking surveys has been added to the text.

Comment 12. "Again, there is a misleading comparison of lifetable vs. proportional mortality approaches to risk characterization. Both make assumptions about the distribution of cause- and age-specific mortality and assume, in some form, constancy of these across calendar time. Since no comparison of the two has been published, it is unclear how they compare in terms of accuracy under the assumptions made."

Response 12. OEHHA accepts that the two approaches use similar assumptions, however we also think that the proportional mortality approach is simpler than the lifetable approach. We do not agree that the text is misleading.

Comment 13. "It is a little confusing that liver and kidney are included in the Smith *et al.* 1992 evaluation. This paragraph needs clarification."

Response 13. The paragraph has been revised to give the individual tumor site contributions to the earlier (1992) and current overall risk estimates.

Comment 14. "Non-cancer effects: The use of the Hanlon & Ferm study of fetal malformations is not well-justified. A more plausible human endpoint, for low-exposures, should be used. Consideration should be given to the Hopenhayn-Rich paper on fetal and infant mortality, to which a relative risk model could be fit, thereby guarding against sensitivity to the changing background rates."

Response 14. We have included a few animal studies in the dose-response analysis of non-cancer effects for comparison. The published study by Hopenhayn-Rich *et al.* (2000) on fetal and infant mortality is of interest to us and we hope that additional data from these authors will allow an adequate quantitative risk analysis based on these data.

Comment 15. "It is not clear on what basis the 20% relative source contribution was made. See earlier concerns about the LED's that are used for cerebral infarct, etc."

Response 15. The 20 percent relative source contribution (RSC) is the default value used when significant non drinking water sources are apparent. Some discussion of this point has been added to the risk characterization. Based on surveys cited in the draft, food is the major source of arsenic and drinking water arsenic could account for 22 to 33 percent of total inorganic arsenic intake. Organic arsenic is also a factor in dietary arsenic. We chose to use the default value as a simplification as it seemed to be similar to these estimates.

Comment 16. "The discussion of noncancer endpoints emphasizes uncertainties that are common to both cancer and noncancer studies far more than in the discussion of cancer studies. In fact, some of the studies of diabetes, cerebrovascular disease, and hypertension are of higher quality than those for cancer in terms of the multitude of individual-level risk factors that were available and the consequent ability to control confounding. The rationale for benchmark dose methodology, in light of the severely

poor fits of several models for key health endpoints, is weak, at best. Serious consideration should be given to the use of the LOAEL."

Response 16. OEHHA thinks that the benchmark dose approach is generally superior to the NOAEL/LOAEL approach in that it uses more of the data in analyzing the dose response. See response to Comment 9.

Comment 17. "The statement "In general animal based values were higher than …" is probably off-base, since the chosen animal-based endpoints (fetal death and gross malformation) are not likely to be sensitive ones in any test species. The issue is probably the selected endpoint, not the species."

Response 17. We have deleted the statement from the final text. However, we think that in general humans are more sensitive to the toxic effects of arsenic than are experimental animals. We agree that the species/endpoints cited are not the best to demonstrate that concept.

Comment 18. "The statement that the smelter studies provide 'strong evidence against expecting sublinearity in dose response' is not accurate or logical. If, as the document argues, errors in the measurement of the exposure are the cause of the supra-linearity, then it is impossible to make any statement about what the shape would be in the absence of such errors, only that it would be less supra-linear than observed, if exposures were lower than estimated due to use of protective gear."

Response 18. We have reworded this to '*some* evidence against expecting sublinearity.'

Comment 19. "The statement about Ferreccio *et al*. is not true: the figure shows that the lowest exposed group has a deficit in lung cancer (figure 4 of this document)."

Response 19. While the lowest of the eight dose groups did show a deficit in lung cancer the overall dose response curve seemed to be more supralinear than linear. If the quantal data are fit by different models using the benchmark dose software of U.S. EPA the best fitting model is the probit with log transformation of dose (X^2 =8.92, df = 6, p = 0.18) versus the linear (X^2 = 20, df = 6, p = 0.003). The rationale for a logarithmic response is not obvious but there is a clear indication of supralinearity in the data set.

Comment 20. "the relatively lower toxicities of MMA and DMA" is an outdated idea, or at the very least, is undermined by the most recent research. It is unclear why the recent findings are repeatedly ignored in this document**.** The subsequent paragraph on methylation patterns needs to be updated in light of recent literature. These papers were described earlier and do not need to be reiterated – instead the relevance to current understanding of DMA carcinogenic promoting activity should be addressed."

Response 20. We have extended the discussion of the methylated metabolites, particularly the DMA carcinogenicity evidence reported by Wei *et al.* (2002). Also see Response to Comment 1.

Comment 21. "The heavy-handed criticism of the study by Morales *et al* does not seem to be warranted. This report is, for the most part, quite clear in the methods used, and the models, other than the MSW model, are clearly presented, standard Poisson regression models. The main critique that can be leveled at this analysis is the lack of biologic rationale for using the log and square root transformations of dose, and the reliance on goodness of fit (although the authors themselves pointed out the weakness of such reliance). The log dose transformation models require the increase in risk to be equivalent for an increase in arsenic from 1 to 2 ug/L as from 50 to 100, or 300 to 600 ug/L. In the absence of mechanistic data supporting this type of relationship, only the identity transformations are plausible. Unfortunately, results of those models are not shown with the use of the southwestern Taiwanese population. However, one of these models is shown for a model using the whole of Taiwan as the comparison population, and this model would serve as a reasonable basis for analysis; it yields an ED01 of 22 and 11 for male bladder and lung cancer, and 21 and 8 for female bladder and lung cancer, respectively."

Response 21. OEHHA does not believe our discussion of the Morales *et al.* (2000) study in the draft is at all "heavy handed." We noted that the results of this study essentially bracket our final risk estimate if the appropriate reference populations are included. However, the Morales study is based solely on the Taiwan data whereas our analysis includes data from Taiwan, Chile, and Argentina.

Comments from U.C. Peer Reviewer #3

Comment 1. "No citations are given documenting the considerable variation in arsenic toxicity found among humans that is described. Although it is undoubtedly the case that such variation exists, citations would strengthen the argument."

Response 1. A citation has been added that addresses human variation in arsenic toxicity.

Comment 2. "The phrase 'metabolic threshold exists over which the body cannot methylate arsenic' appears overstated. Later the paragraph states that 'the percentage excreted as MMA remains virtually unchanged', which means methylation is occurring. Later the document goes to considerable lengths to dispel the hypothesis that a threshold for methylation exists. Thus, instead of referring to a threshold where the 'body cannot methylate arsenic', the text would be more accurate to say something like 'where methylation appears less complete.'"

Response 2. Comment noted and suggested wording adopted.

Comment 3. "That arsenic can have effects on human blood has been demonstrated now in two studies consistent with oxidative stress: Wu *et al.* (2001) Env Hlth Perspect 109:1011-1017; Pi *et al*. (2002) Env Hlth Perspect 110:331-336."

Response 3. Both studies noted and now cited in the revised text.

Comment 4. " In line 2, 5 μM arsenite is referred to as 'subtoxic'. What does this mean? For short times cell lines can withstand this concentration, but it is lethal to many after a week or so."

Response 4. The term subtoxic applies only to the experimental conditions employed. The sentence has been revised for clarification.

Comment 5. "Line 5 refers to results with DMA at 0.2-5 mM. While the present document accurately conveys interpretations of results as reported by the experimenters themselves, one bothersome aspect of MMA and DMA studies that the original reports do not address is purity. In studies with negative results this may not be a problem, but in studies with positive results one must keep this in mind. For example, MMA is commercially available in 98% purity. When it is used at 1mM concentration (or above), an impurity could be present at 20 μM (or more). …If the impurity were inorganic arsenic, interpretation of the results could be greatly affected. Since numerous reports are cited in the text (e.g., page 42, par 1) and listed in tables (e.g., Table 5), mention of this problem should be made prominently somewhere. Of course, the logical rejoinder could be made that MMA+5 becomes toxic only at high mM concentrations because human MMA+5 to MMA+3 reductase has a Km in the high mM range (Zakharyan *et al.*, [2001] Chem Res Toxicol 14:1051-1057)."

Response 5. Comment noted. A paragraph has been added discussing this potential problem. The high concentrations and doses of DMA employed in both in *in vitro* studies and whole animal cancer bioassays are a source of concern. Some have argued that DMA may be the ultimate carcinogen but this idea is difficult to square with the dosimetry. New animal models based on arsenite carcinogenicity may shed light on the relative roles of the arsenic metabolites.

Comment 6. "The interesting results of Kaltreider *et al.* (2001) are cited and provide a potentially important aspect of arsenic action. The cell type or species dependence of this effect is important, however. A negative result in human keratinocytes suggests limitations on its generality (Jessen *et al*. [2001] Toxicol Appl Pharmacol 174:320-311). Species or cell variation in effects on transcriptional coactivators or corepressors (Hong *et al*. [2001] Molec Cell Biol 21:7171-82) could rationalize such differences."

Response 6. A discussion of the Jessen *et al*. (2001). and Hong *et al*.(2001) papers has been added to the human toxicology section.

Comment 7. "In Tables 5 and 9, a later report updates the citation of Kanchinkas *et al*. (1997) to give concentration dependence information (EC50 ≈ 1 μM) and includes normal epidermal cells…"

Response 7. Table entries updated with new information.

Comment 8. "The rationale for amplification of an oncogene being late is not given. Presumably this statement follows from observations that gene amplification is very difficult to detect in normal cells but easier as the cells progress to malignancy (Wright *et al.* [1990] Proc Natl Acad Sci USA 87:1791-1795)."

Response 8. Wright *et al.* (1990) is now cited in the revised draft.

Comments from the U.S. EPA Office of Water

Comment 1. "p. 2, 5th para - Rewrite sentence starting "That which is absorbed..." since: 1. most of the organic arsenic (arsenobetaine) is excreted unchanged, or 2. the arsenocholine may be broken down, but not to "less toxic forms" as the parent compound is not very toxic and 3. the inorganic arsenic is activated to the trivalent metabolites which are the putative active agents. See your comment in second para on page 3. I think that the consensus now is that the trivalent methylated metabolites are the toxic forms."

Response 1. Paragraph rewritten.

Comment 2. "p. 3, 3rd para - "The levels of food that most people ingest in food and water (ca. 50 µg/day)..." This needs to be revised for the following reasons: 1). Are you implying that the As in food is toxic? With your 10^{-6} PHG of 4 ppt, that would mean that the 50 ppb in food would be 1.25 X 10^{-2} risk. If you limit the As to inorganic As (10 µg/day), it would still be approximately 2.5 X 10^{-3} risk. I think you really need to discuss the As species in food and what it means to the arsenic problem. (Note, I know the document stated on the top of p. 2 that the "actual risks of low-level exposure are unlikely to exceed these risk estimates...", but many people use these numbers as thought they were exactly correct.) The State of California is also using the PHG to set a level for arsenic in drinking water - as close as possible to the PHG.). 2). There is a large difference in the toxicity of inorganic arsenic in food and, say, arsenobetaine in fish, but total arsenic in included in the 50 µg/day figure 3). The data that you cite applies primarily to the US. For example, the article by Schoof et al. (Hum Ecol Risk Assess 4:117-135, 1998: Dietary arsenic intake in Taiwanese districts with elevated arsenic in drinking water) on arsenic in Taiwanese food states that the average consumption of inorganic arsenic in the diet of people in the Blackfoot region of Taiwan (50 µg/day) is much higher than in the US. Incidentally, this paper is not in your ref list."

Response 2. Organic arsenic in food is much less toxic than inorganic arsenic in drinking water. This is clearly pointed out in the PHG document, but risk assessment of arsenic in food is beyond the scope and mandate of the PHG. Our PHG document cites the recent studies by Meacher *et al.* (2002) and Schoof *et al.* (1999) on inorganic arsenic intake in the U.S. population.

Comment 3. "p. 17, Excretion - The drinking water studies do not account for potential exposure from food (could be significant) or air and dermal exposures (low, except in

specific situations such as rice farming if the farmers are wading in water containing arsenic)."

Response 3. We agree that food can be a significant source of arsenic exposure. However, exposure from food does not appear to be a major confounder for these particular studies, because there is no great disparity in the studies of arsenic excretion that could be explained by alternate and coincident sources and routes of exposure. For example, the studies with radiolabeled As were done following overnight fast, which would tend to minimize food sources.

Comment 4. "On p. 20, 2nd para - Under Physiological/Nutritional Role - You state that caution needs to be exercised in assuming a nutritional role for As based on animal studies and state that "Arsenic is a proven human carcinogen, but is not readily carcinogenic in animal species studied." and "Thus, animals would appear to need more arsenic and be more tolerant..." However, at the bottom of p. 1, you state that similar risk estimates [to risk estimates from human studies] were calculated from a mouse bioassay using prenatal exposure to As. You can not argue the animal data one way for risk assessment, but another way for nutrition without completely establishing credible reasons for doing it. The present way makes it seem that you are picking and choosing data to suit you view."

Response 4. It is true that historically animal cancer bioassays with arsenic have been largely negative. Also, in general, animals seem more resistant to the acutely toxic effects of arsenic than humans. A recent transplacental assay, which exposed mice to arsenic during critical phase of organogenesis, gave positive results in offspring without further treatment. While surprising, OEHHA believes the data to be relevant and worth citing. OEHHA does not believe that this single finding undercuts the large group of human studies showing arsenic carcinogenicity and other adverse health effects. Staff have derived a potency from this study in connection with our state mandates for children's health (SB25, Children's Environmental Health Protection Act of 1999). The analysis may help inform us as to the carcinogenic potency and mechanisms in animals, and is not inconsistent with the human data. However, OEHHA does not think that the animal-based potency is superior to the human-based value and the latter is used as the basis of the PHG.

Comment 5. "pp. 21-22. I would not consider the Petrick et al. (2001) protocol to be a definitive - nor necessarily applicable - LD_{50} study for As since humans do not receive As via i.p. injection. Say that the data "suggest," not indicate that the metabolite is more acutely toxic than the arsenite."

Response 5. Suggested revision made.

Comment 6. "pp. 23-29, Genetic Toxicity - I think there should be some interpretation of the results. The data indicates that various forms of As act via indirect methods, e.g., enzyme inhibition, except for the Mass study using the trimethylated metabolites. Recently, Nesnow (Chem Res Toxicol 15:1627-1634, 2002) showed that even these

compounds exerted their effects via indirect methods (Reactive Oxygen Species). This should be mentioned and discussed."

Response 6. This is a good point. An overview has been added at the end of this section including a description of Nesnow *et al*. (2002).

Comment 7. "p. 58, Arsenic in Chemotherapy - Descriptive only. Are there any data that might shed light on the carcinogenic effects of As?"

Response 7. The current limited data do not provide any major insights into the carcinogenicity of arsenic. Since the mechanism(s) of arsenic carcinogenicity is unknown it is difficult to say if the mechanisms of arsenic chemotherapy and carcinogenesis are related."

Comment 8. "p. 59, 4th para - You should mention that the median exposure interval between from the metal analysis and conception was up to 1.6 years (Aschengrau et al., 1989, p. 284). I think that the report has serious flaws and they should be mentioned."

Response 8. The document was changed as suggested.

Comment 9. "p. 82, 2nd para - The As exposure in the control population 1 to 17 µg As/L) was measured by the Natelson method (see Tseng, 1977, p. 118) and the method is only accurate above 40 µg As/L (Greschonig and Irgolic, In: Arsenic and Health Effects, edited by CO Abernathy et al."

Response 9. The text has been revised and the citation added.

Comment 10. "p. 99, 2nd para - Bates et al. gives reasons for the potential lack of bladder cancers in the Utah population. What about the recent Steinmaus et al. (2003; Amer. J. Epidemiol. 158(12):1193-1202: Case-control study of bladder cancer and drinking water arsenic in the western United States.) paper which finds no increase in bladder cancers. The authors state "Overall, no increased risks were identified for arsenic intakes greater than 80 µ/day... These risks are below predictions based on high dose studies from Taiwan." They also state that "These data provide some evidence that smokers who ingest arsenic at concentrations near 200 µg/day may be at increased risk of bladder cancer."(p. 1193). From this statement, one would assume that if you were a non-smoker, you would have no increased risk of bladder cancer at "near 200 µg/day." With a proposed PHG of 4 ppt, this paper needs to be discussed in the risk assessment section of the document."

Response 10. A description of this recent study has been added to the Human Cancer section. While this study is interesting, we don't think it can be used for quantitative risk assessment. In any event it would not replace our current unit risk value, which is based on lung and bladder cancers. A mention of this study has also been added to the section on Calculation of the Proposed PHG.

Comment 11. "On p. 109, 2nd para, l. 3 - there is a statement that "evidence showing arsenic accumulation in the lungs...," while on p. 2. 5th para, l. 3 - you state "Arsenic does not have a tendency to accumulate in the body at low environmental exposure levels." I assume that the mummies in Chile with arsenic in their lungs were exposed to higher than normal environmental arsenic levels. Every analysis of metals in the body reveals deposition of arsenic. In addition, as stated on this same page (last para), you state that arsenic (in the +3 valence state) is known to bind to sulfhydryl groups. You need to revise these sections."

Response 11. There is clearly As deposition in the lungs and other tissues. In kinetic studies with radiolabeled As there appeared to be a lack of accumulation as seen with certain other metals.

Comment 12. "After earlier stating that there are differences between humans and animals in responses to arsenic and metabolism of arsenic, I would not use a animal study (Waalkes et al., 2003) to support the human quantitation studies."

Response 12. As discussed in the response to Comment 4, OEHHA believes the new animal data are worth presenting.

Comments from the U.S. EPA Office of Research and Development

Comment 1. "…the OEHHA approach taken for cancer dose response assessment is simplistic in comparison with that taken by the National Research Council (NRC). The approach may be too simplistic, however. The OEHHA approach fits a regression model to the relative risks for different concentrations of arsenic from different studies without consideration of the age of the cohorts or any other variables that may be relevant. Such pooling of the data, without considering the comparability of the different studies, is inappropriate, especially when case control and cohort studies are combined in the analysis."

Response 1. The comment is correct in that our approach was simpler than that of the NRC or that of Morales *et al.* (2000). However, OEHHA believes that our analysis was adequate and the resulting unit risk values are quite close to those obtained by the NRC, albeit higher than those of U.S. EPA in their Arsenic Final Rule of 2001.

Comment 2. "Although there are many recently published papers on arsenic, one that will likely receive considerable attention in the public debate over arsenic is the paper by Steinmaus *et al.* ….in which the authors find no increased risks for arsenic intakes greater than 80 μg/d and claim the risks are below predictions based on high dose studies from Taiwan. You may wish to include this paper in your review."

Response 2. This article has been included in the latest revision of the PHG technical support document. The authors did find a significant dose related effect in *smokers* with exposures greater than 80 μg/d with an adjusted odds ratio of 3.67 (95 percent CI: 1.43-

9.42, linear trend, $P < 0.01$). This study, while interesting, is based on very low numbers of subjects and did not assess lung cancer, the major cancer site in the OEHHA risk assessment. Due to the low numbers we think the study is inadequate for a quantitative risk assessment. As noted in our PHG document, the estimated cancer risks at low exposures may be lower than indicated by the unit risk value or zero.

Comments from Clean Water Action

Comment 1: " On behalf of our 20,000 California members, Clean Water Action commends OEHHA for its development of a Public Health Goal for arsenic at 4 ppt. This protective level makes great strides towards safeguarding the health of millions of Californians affected by arsenic contamination of their drinking water. We praise OEHHA for considering the vast public health implications of the arsenic standard in its decision-making process and designing a PHG based on the best available science."

Response 1: The proposed PHG of four ppt represents a goal, which likely cannot be met in the near future. The state Department of Health Services will evaluate technical and economic limitations and set a regulatory standard as low as is feasible.

Comments from the National Resources Defense Council

Comment 1: "The document fails to acknowledge the apparent lack of a threshold for non-cancer health effects."

Response 1: OEHHA does not fully agree with the comment. Our risk assessment methodology, like that of the U.S. EPA, has approached non-cancer endpoints with the assumption that dose responses either have a clear no effect level or marked non-linearity at low dose. In contrast, most carcinogens are treated assuming low dose linearity with no practical threshold. In recent years the methodology of cancer and non-cancer dose response assessment has become more similar through the use of benchmark dose response methods (BMR). These methods allow the projection of risks for non-cancer endpoints as well as cancers. You will note that in the summary table of the Calculation of Health Protective Drinking Water Concentrations Based on Non-Cancer Toxicity (Table 18 in the public review draft) we have listed risk levels together with the uncertainty factors we applied to the various studies. Thus the reader who assumes no threshold can readily judge the projected risk of the values we calculated using uncertainty factors. At this point there is little theoretical basis for treating non-cancer endpoints as low dose linear, although empirical data might support such an approach in a number of cases. OEHHA is continually updating its risk assessment methodology and may adopt linear low dose approaches for some non-cancer effects on a case-by-case approach as warranted.

Comment 2: "The document fails to discuss the risks to infants and children."

Response 2: A number of studies relevant to infant and child risk are described in various parts of the draft text. We have revised the draft to summarize these in a new section on "Vulnerability of Infants and Children." In addition we have added a revised

calculation of a health-protective value for developmental neurotoxicity based on an upper percentile of the distribution of child water intake rates.

Comments from Bergeson & Campbell, P.C. for MMA Research Task Force Three

Comment 1: "The studies on which the proposed PHG is based do not address organic compounds and for this reason cannot legitimately be the basis for regulatory standards that apply to organic arsenic compounds."

Response 1: Questions on the regulation of arsenic in drinking water should be directed to the California Department of Health Services (DHS), which is responsible for developing the state MCL based on the PHG and other factors. OEHHA does not agree that the proposed PHG addresses only inorganic arsenic, although that is the form most commonly found in drinking water supplies. As noted in the document, ingested inorganic arsenic in humans and most mammals is reduced and methylated to mono and dimethyl organic forms, which are largely excreted into the urine. For this reason exposure to inorganic arsenic via contaminated drinking water will always entail internal exposure to its organic metabolites. Recent studies have established that far from being benign detoxification products of arsenic metabolism, these compounds may be either more toxic than arsenite (As^{III}), e.g. MMA^{III}, or may be carcinogens in their own right, e.g., DMA in rat urinary bladder. The latter compound as DMA^{V} or cacodylic acid was used historically as an agricultural herbicide and might find access to drinking water supplies via agricultural runoff into surface waters. In our view, any regulation of arsenic in drinking water should apply to total arsenic and not be limited to inorganic or to specific organic species. We believe the draft PHG provides ample scientific support for this approach. However, as noted above, DHS will determine the analytical methodology applicable to the regulation of arsenic in drinking water.

Comments from BP/ARCO, Integral Consulting Inc., Rosalind Schoof

Comment 1: "The discussion of Production and Uses on Page 5 refers to data from 1987. This is extremely dated information is inadequate to support the proposed action."

Response 1: OEHHA acknowledges that some figures given here are more than a few years old. However, these are the most recent data that we found. The production figures are peripheral to our assessment of public health risks from arsenic. For the PHG, OEHHA's primary concern is with toxicity of naturally occurring arsenic in drinking water.

Comment 2: "The discussion of dietary intake is missing several recent references, including a reference to the only market basket survey to date that reported concentrations on inorganic arsenic in foods consumed by Americans (Schoof *et a*l. 1999a, Schoof *et al.* 1999b). … These references should be reviewed by OEHHA, and then this section should be revised to focus on the intake of inorganic arsenic, the more problematic form from a human health perspective."

Response 2: The section on Food has been revised to include a description of the results from Schoof *et al*. (1999b), the Total Diet Study of the Food and Nutrition Board (2002), and the Meacher *et al.* (2002) Monte Carlo study. The study of Schoof *et al.* (1999a) does not include food consumption data, which would allow the estimation of arsenic intake for various diets. The Meacher *et al*. (2002) study estimated lower levels of 3-4 μg/day from all sources for the U.S. population, and 9-10 μg/day for the western states, approximately 50 percent derived from food sources. Schoof *et al.* (1999b) note that the intake of inorganic arsenic reported by Yost *et al.* (1988) of 8-14 μg/day is unlikely to be exceeded based on their market basket survey. We do not agree with the commenter that inorganic arsenic is the only form of arsenic that presents concern from a human health perspective. Please see the response to comment from Bergeson & Campbell above.

Comment 3: "The discussion of arsenic concentrations in water should make clear that in most case the occurrence of water in drinking water supplies is a natural occurrence. It is important that the public understand that arsenic is present in all water, including sea water, at some level, and that complete removal of arsenic from all water supplies is not feasible or necessary for the protection of human health."

Response 3: OEHHA thinks that the discussion of arsenic occurrence in drinking water supplies is adequate for the purpose of the PHG technical support document. The primary focus of the document is to estimate concentrations in drinking water that present negligible risk of adverse health effects over a lifetime of exposure. Evaluation of the technical and economic feasibility of an arsenic drinking water regulation (i.e., an MCL) is being conducted by the California Department of Health Services.

Comment 4: "The updated discussion of intake from diet and drinking water should be used to revise the source contribution term used in the derivation of the proposed PHG (page 158). Based on the study of Meacher *et al.* (2002) drinking water contributes much more than 20% of background arsenic intake."

Response 4: Our adoption of the default value of 20 percent for relative source contribution (RSC) is based on the estimate of inorganic arsenic intake from Yost *et al.* (1998) of 8-16 μg/day for North American diets and a median arsenic concentration in drinking water of 2 μg/L for the 1995 survey of California water agencies. These figures give a range of 25 to 33 percent for an estimated RSC. Since this estimate addresses only inorganic arsenic and drinking water and food as sources, there is uncertainty in the estimate. OEHHA thinks that the 20 percent default is a reasonable health-protective estimate. Also it should be noted that the RSC applies only in calculations of health-protective values of non-cancer endpoints. Since the proposed PHG is based on lung and bladder cancer, the RSC plays no role in the calculation of the proposed four ppt value.

Comment 5: "The study of Wester *et al.* (1993) is missing from the discussion of dermal absorption of arsenic on page 11."

Response 5: The results of Wester *et al.* (1993) in Rhesus monkey (*in vivo*) and human cadaver skin (*in vitro*) have been added to the discussion of dermal absorption of arsenic.

Comment 6: *The Chilean and Argentine ecological studies have even more limited exposure data than was available for the Taiwanese studies, and suffer the same limitation of characterizing highly variable exposures among groups identified as low, medium and high exposure groups. ...these studies do not provide a credible quantitative basis for dose-response assessment for ingested inorganic arsenic, and hence, may not be relied upon to support the proposed PHG.*

Response 6: OEHHA acknowledges that all of the human arsenic epidemiology studies suffer from various defects not limited to the usual problem of less than desirable exposure data. Rather than confining our assessment to the Taiwan data set, as did the U.S. EPA and the National Academy of Sciences (NAS, 2001), we think an advantage is gained by combining the data sets. Overall our results in terms of dose-response are very similar to those obtained by the NAS. We understand that not everyone agrees with our approach, nevertheless we think it is valid enough for our purposes.

Comment 7: "OEHHA relies heavily on the case-control study of arsenic –exposed populations in Chile by Ferreccio *et al*. (2000) without adequately acknowledging some significant limitations described by the authors."

Response 7: The Ferreccio *et al*. (2000) study is the only available study with exposure data covering a lifetime of arsenic exposure. We believe it is appropriate to use this study despite its limitations. As noted in response 10 above, there is no perfect study of arsenic-induced cancer in humans. We think our approach of combining studies is the best available way to limit the defects of each.

Comment 8: *The Utah study by Lewis et al. (1999) is easily the most important study conducted in the U.S. …the study found more evidence of protective effects of arsenic against both non-cancer and cancer endpoints than detrimental effects and, because of a multiple comparisons effect, there is the potential that one or more positive results may have occurred by chance alone. OEHHA should note that this study provides support for a lack of adverse effects when drinking water arsenic concentrations are below 50 to 100 μg/L. Further, the findings of this study are in direct conflict with OEHHA's discussion of a possible supralinear dose-response for arsenic-induced cancers in the low dose range.*

Response 8: OEHHA does not share the commenter's view of the utility of Lewis *et al*. (1999) for risk assessment. We have noted the limitations of the study in the document (pages 99-100). The study does indicate an apparent arsenic-induced increase in prostate cancer. We don't agree that the study is of any use to support arguments over the shape of the dose response relation for the major sites of lung and urinary bladder.

Comment 9: "OEHHA's quantitation of cancer risks is inappropriately weighted to over-represent the studies of Argentine and Chilean populations. The National Academy of Sciences (NRC, 2001) concluded that the most reliable studies available for quantitation of cancer risks from ingestion of arsenic in drinking water are the studies conducted on populations in Taiwan. These studies are viewed as more reliable due to both their large population size and the length of follow-up."

Response 9: The National Academy of Sciences (NAS) also concluded that the study from Chile, despite its limitations, might augment those from Taiwan to assess cancer risk. That has essentially been our approach. The unit risks we derived for lung and bladder cancer are very similar to those of the NAS, although we could not derive a separate value for bladder cancer.

Comment 10: "The proposed PHG should be withdrawn and be replaced with one based on a unit risk value derived from the Taiwanese studies, consistent with the recommendations made to USEPA by the National Academy of Sciences (NRC 2001)."

Response 10: As noted in response to comment 9, our unit risks are similar to those derived by NAS but 4 to 10 times higher than those derived by U.S. EPA, although both organizations used the same Taiwan data set for their analyses. As noted elsewhere in these responses to public comments, we think an analysis of all appropriate data gives a better estimate of overall unit risk for the key target tissues.

Comment 11: "OEHHA has proposed an arsenic PHG of 0.004 μg/L, a value that is orders of magnitude below arsenic concentrations in any natural water supply. This fact means that OEHHA has extrapolated arsenic cancer risks to concentrations below those experienced by the control populations in the studies used to establish arsenic carcinogenicity. This outcome of OEHHA's analysis is neither scientifically nor logically supportable."

Response 11: OEHHA disagrees with the comment. OEHHA is complying with California law, which requires a PHG that, based on current scientific evidence, presents negligible risk of adverse health effects over a lifetime of exposure. The law specifically prohibits OEHHA from consideration of economic, technical or other societal factors. These latter factors are taken into account in developing the MCL regulatory standard by the California DHS. The law also requires periodic (5 years) updating of the PHG with respect to current supporting science.

Comment 12: "CalEPA neglects to mention an important negative European epidemiology study. Buchet and Lison (1998) report a study showing no increase of cancer mortality in a Belgian population with moderately increased arsenic intake. … These findings are highly relevant to OEHHA's analysis of low dose risks, and specifically should be described providing support for a sublinear dose response …etc."

Response 12: The PHG document does cite Buchet and Lison (2000) on page 106 of the review draft. Unfortunately there are many possible explanations for negative

epidemiological findings. Since this study does not outweigh the numerous positive epidemiological studies of arsenic exposure and induced cancer at multiple tissue sites by multiple routes of exposure, it is difficult to use in quantitative risk assessment. Since there is at present no convincing mode of carcinogenic action that clearly demonstrates low dose nonlinearity, OEHHA is obligated to adopt a linear low dose approach. It should be noted that some studies (e.g., Ferreccio *et al.*, 2000) indicate a low dose supralinearity of response.

Comment from Mr. George Roy

Comment 1: "The 4 ppt standard would cost us huge sums of money with no proven benefit in return. Its impact are extensive and complex. Measurements of this level presents interesting questions."

Response 1: The proposed PHG is not a regulatory standard but rather a goal. It occupies approximately the same position in California drinking water regulation as the federal Maximum Contaminant Level Goal (MCLG) does in national regulation. The national MCLG for arsenic is zero. Rather than use zero for the proposed PHG, we have estimated a negligible risk level. The California DHS will likely set the MCL standard somewhere within the bounds of the current reporting level of 2 ppb and the new national MCL of 10 ppb. Their evaluation will take into account cost, technical feasibility, and other societal factors. The commenter is correct in noting the probable high cost of any new arsenic regulation but this is an issue the DHS will address. With respect to benefits, environmental public health regulations do not require a demonstration of specific benefits before reasonable restrictions are implemented. The expected benefits are reduced cancer and non-cancer risks, but with the exception of skin effects, arsenic's adverse health effects are indistinguishable from common cancers and other chronic diseases, which cause major mortality and morbidity (e.g., lung cancer, vascular diseases, and diabetes).

Comments from the Grocery Manufacturers of America, by Jay Murray

Comment 1. "The PHG Report excludes two studies that current risk assessment practices would have included – Ferreccio *et al.* and Tsuda *et al*. The PHG Report should be revised to include these two studies."

Response 1. The PHG draft did include both studies referred to above, namely Ferreccio *et al.* (2000) "Lung cancer case control study in Chile identifies a strong exposure-response trend with arsenic concentrations in drinking water" Epidemiology 11:673-679; and Tsuda *et al*. (1995) "Ingested arsenic and internal cancer; a historical cohort study followed for 33 years" Am J Epidemiol 141:198-209. In Tables 8 and 9 and Figures 4 and 5 the document details our analysis of the Ferreccio *et al.* study. To the best of our knowledge, all major studies and significant epidemiological data have been included in our risk assessment.

Comment 2. "Information on the possible modes of action of arsenic indicate that a sub-linear or threshold dose-response curve is more probable than not. Current risk assessment practices require the use of a threshold model when the threshold approach is the more probable explanation of dose response. In the case of arsenic, the mechanistic data favor sub-linearity, and the data utilized for linear extrapolation were particularly weak."

Response 2. The comment appears to misinterpret U.S. EPA guidance on carcinogen risk assessment. There is currently no acceptable mode of action established for arsenic and while arsenic compounds are not typical mutagens they do exhibit a wide range of genotoxic actions. In fact there are likely to be multiple modes of action for arsenic. Since there is at present no convincing mode of carcinogenic action that clearly demonstrates low dose nonlinearity (threshold), OEHHA is obligated to adopt a linear low dose approach. It should be noted that some studies (e.g., Ferreccio *et al.*, 2000) indicate a low dose **supra**linearity of response. OEHHA acknowledges that the epidemiological data have limitations for extrapolation to low levels and that additional studies at lower exposure levels with larger populations would be desirable, notwithstanding the potent carcinogenic effects observed at higher levels.

Comment 3. "Data exist for arsenic exposures below 80 μg/L, but no such data were utilized in the PHG risk assessment. This represents a departure from current risk assessment practices, which call for assessments to consider data in the relevant low-dose range, especially when mechanistic information suggests sub-linearity of the dose-response curve may be plausible. Thus, the low-dose data from Ferreccio *et al*. and Tsuda *et al.*, should be included in the risk assessment, as noted above, for this reason as well."

Response 3. These studies were incorporated into the arsenic PHG document, with analysis of dose-response data as noted in Response 2. Also please note Figure 4 in the PHG document which fits a linear regression to the Ferreccio *et al*. lung cancer vs. arsenic water concentration data set. When a benchmark response analysis is applied to this data set (BMDS v. 1.3.2, U.S. EPA), the dose response data show a much better fit by a supralinear model (probit, $X^2 = 8.92$, d.f. = 6, P = 0.18) than by a linear model (quantal linear, $X^2 = 20.0$, d.f. = 6, P = 0.003). There simply is no convincing evidence for sublinearity or a threshold, and as our document concludes, the data in the key studies are not good enough to distinguish between linearity and sublinearity of low-dose response.

Comment 4. "Furthermore, the PHG report should note more prominently the U.S. studies of arsenic in drinking water. Studies in U.S. populations exposed to arsenic in drinking water have not identified cancer increases (e.g., Morton *et al.*, 1976; Southwick *et al.*, 1981; Valentine *et al.* 1992). Also, the U.S. data in the National Cancer Institute's SEER database could have provided data on whether any increase in cancer mortality is observed in areas of the U.S. with higher concentrations of arsenic in drinking water. To date, no increase in cancer rates due to arsenic in drinking water have been reported in studies in the U.S."

Response 4. Arsenic epidemiology studies in the U.S. have utilized limited populations, usually with relatively low exposures; the dose-response data do not contradict the larger, higher-exposure studies conducted elsewhere. The PHG document includes a discussion of Lewis *et al.* (1999), who investigated an arsenic exposed cohort assembled from an earlier study (Southwick *et al.*, 1983). This was probably the most important U.S. study available at the time of our risk assessment. It indicated an apparent dose response relationship for prostate cancer among arsenic-exposed males. However, it was of little use for the main cancer sites of lung and bladder and had several methodological problems that made the results difficult to interpret. More recently, Steinmaus *et al*. (Am J Epidemiol 158:1193-1201, 2003) observed increased bladder cancer in arsenic-exposed smokers with arsenic intakes greater than 80 μg/d (median 177 μg/d, 88 μg/L). This was a case-control study in Nevada and California with 181 cases and 328 controls. Irrespective of the various uncertainties of low dose extrapolation, the difference between the exposures causing cancer and other adverse effects and the current exposure standards (MCL of 50 μg/L, being decreased to 10 μg/L) is small, and would be considered inadequate using the "margin of safety" approach.

Comment 5. "The contribution of arsenic in food was not taken into account in the Taiwan study. The PHG risk assessment should adjust the Chen data to reflect greater arsenic in the diet of the high exposure group, and it should adjust the results further to apply them to California, where less arsenic is found in the diet."

Response 5. This issue was discussed in the Risk Characterization section of the PHG document. Little information is available concerning arsenic concentrations in food sources in the study populations. All evidence to date suggests that the overriding exposure to inorganic arsenic was from drinking water. However, local contamination of food sources could lead to a small overestimation of the cancer risks if the concentration in the food is correlated with that in local water sources. Alternatively, if food is widely distributed so that food arsenic is not correlated with that in local water sources, then the slope of the relative-risk dose-response relationship would not be affected. Note that the food intake of inorganic arsenic in the U.S. does not impact the cancer potency estimates we derived because we have calculated the *incremental* lifetime lung and bladder risks resulting from the ingestion of inorganic arsenic in the drinking water. Overall, there is no basis for attributing much uncertainty in arsenic risk estimates for drinking water to arsenic contamination of food.

Comment 6. "One critical decision used to derive the draft PHG is: "the y-intercepts were forced through a RR of 1 for 0 μg/L." That is, it is assumed that any concentration of arsenic in drinking water above zero poses an increased RR (relative risk) of cancer. Once again, the current practice is to examine all the data on mode of action before making any decisions about the dose-response curve. As discussed earlier, the most likely modes of action of arsenic suggest a non-linear dose-response curve. The current risk assessment practice is to base the decision on the best available science. The science certainly does not tell us that the y-intercept passes through a RR of 1 for 0 μg/L."

Response 6. As noted in the Response to Comment 2, the data have been analyzed by standard methods. OEHHA does not agree that a mere suggestion of a possible non-linear mode of action (MOA) is a sufficient basis for adopting a nonlinear extrapolation approach for arsenic risk assessment in support of a drinking water standard applicable to 35 million Californians. As noted above and at great length in the PHG document, there is no established MOA for arsenic carcinogenesis or its serious noncancer effects. OEHHA acknowledges uncertainties in the low-dose extrapolation of cancer risks. However, at the present time and in accordance with "the most current practices of risk assessment" as outlined in the Guidelines for Carcinogen Risk Assessment (U.S. EPA 1996, 1999) we have adopted a linear low-dose approach for arsenic. This assumes zero effect at zero dose, i.e., a relative risk of 1.0 at zero dose. This approach is consistent with those employed by U.S. EPA and the National Academy of Sciences in their risk assessments of arsenic, although each of the three assessments relied on a somewhat different group of studies and/or methodologies.

Comment 7. "There is an unusually high degree of uncertainty associated with the risk assessment of arsenic. To its credit OEHHA has done an excellent job of describing these uncertainties on pages 171-182 of the PHG Report …Unfortunately, the two Summary sections of the PHG Report do not clearly and accurately convey the high degree of uncertainty underlying the estimated cancer risk and the draft PHG. PHG documents have a broad audience beyond scientific experts. … Therefore, it is critical that the Summary sections of the PHG Report communicate in plain English the extremely high degree of uncertainty associated with the draft PHG."

Response 7. OEHHA has produced risk assessments for nearly 70 PHGs and we do not agree with the comment that the arsenic PHG incorporates an "unusually high degree of uncertainty." Arsenic and arsenic compounds are proven human carcinogens and the risk assessment is based largely on human data. Most risk assessments conducted by OEHHA rely on animal data with little or no relevant human data. There is far more uncertainty extrapolating to a negligible risk exposure in humans based on rodent tumors in a high dose bioassay than from human epidemiology with exposures within an order of magnitude of current standards. The estimated risk of arsenic in drinking water is very high relative to other regulated drinking water contaminants based on any of the recent risk assessments (OEHHA, U.S. EPA, or NAS). We acknowledge that the greater the extrapolation (i.e., to low ppt levels), the more uncertainty there is about the actual risk.

The PHG document is a technical support document intended to define an acceptable exposure level based on current science and to be updated about every five years. For the general public, OEHHA provides other documentation in support of the PHGs that is less technical e.g., Guide to Public Health Goals (PHGs) for Chemicals in Drinking Water: A Fact Sheet (pdf file); Proposed Public Health Goal for Arsenic in Drinking Water – A Fact Sheet, both available online at www.oehha.ca.gov/public_info/facts/index.html. Also OEHHA provides local water officials with Health Risk Information for Public Health Goal Exceedance Reports, which documents key chemical health effects in simple non-technical language and compares PHGs with other relevant standards and goals.

Comment 8. "Since food significantly surpasses water as a source of exposure to arsenic in the U.S., one would expect public health officials to have suggested a change in diet if the risk assessment contained in the PHG Report were considered reliable. The absence of such action suggests a lack of confidence in risk extrapolation to the dose range relevant to the draft PHG. Furthermore, the PHG Report should signal that foods with trace amounts of arsenic in excess of the PHG, many of which promote health, should not be avoided. Among the reasons that should be expressed is the substantial uncertainty associated with the PHG and the overall nutritional benefits of the foods which contain arsenic."

Response 8. OEHHA believes that the estimation of arsenic risk in drinking water involves less uncertainty than in most risk estimates. Most of the arsenic in food is organic arsenic of less certain risk than inorganic arsenic in drinking water. Compared to water-borne inorganic arsenic, food arsenic is more variable and food sources more diverse than water arsenic. This probably results in more variable dosimetry from food than from water. There are no epidemiological studies showing an association of food arsenic intake and adverse effects, in contrast to water arsenic where there are several studies from different countries. Specific advice on foods is beyond the scope of the PHG document. While food arsenic is taken into account for noncancer health effects (via the relative source contribution consideration), it plays no role in the cancer potency (unit risk) and the PHG value developed.

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