Responses to Major Comments on Technical Support Document

Public Health Goal
For
Selenium
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 selenium. The comments from the first three invited reviewers, received in 2006, are based on the prerelease review draft of 2006. The comments of the last commentator, received in May 2010, are based on the first posted draft of 2009. Changes have already been made in response to these comments, and have been incorporated into the final version posted on the OEHHA web site. 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 on the prerelease draft 2006

Comments from Raymond F. Burk, MD, Vanderbilt University

Comment 1: "The document is a very ambitious attempt to cover virtually everything that is known about selenium in biology. This includes normal biochemistry, metabolism, and function of selenium as well as its toxicology. It is, nevertheless, a draft document and needs extensive improvement before it can be finalized. I will make some general comments that apply to more than one section of the document and then list some specific problems. Because of the length of the document (300 pages single spaced) I cannot comment on everything that needs correcting."

Response 1: We agree with the comment regarding the attempt to cover the extensive database on selenium as selenium is one of the substances with the largest available scientific database. It is estimated that there are more than 100,000 publications in the past 50 years, and more than 1,000 new publications have continued to appear each year in the past decade. Due to the narrow range between the essential doses and the toxic doses, our prerelease draft included an extensive review of both essentiality and toxicity as well as selenium status in various populations relating to health and diseases, including dietary supplementation. In response to reviewers' comments and in consideration of simplicity and clarity, we have greatly shortened the document and simplified the scope to more specifically address selenium toxicity, directed toward development of the PHG.

Comment 2: "Many papers are cited and presented in capsule form. For the most part, these capsules lack critical evaluation and accept the conclusions of the authors. Moreover, it is not always clear how the papers presented connect to the intellectual process of determining the PHG. I recommend that all papers cited be considered critically and be integrated into the discussion and arguments (or be ignored if they do not contribute). This will result in a much shorter document."

Response 2: We have greatly condensed and tightened up the document and the resulting document is about half the length of the original version.

Comment 3: "The document switches back and forth between moles and grams. For ease of reading, one should be used and the other can be given in parentheses if that is desired."

Response 3: This has been modified. The units have mostly been changed to grams.

Comment 4, page 1: "The findings listed as effects of selenosis, with the exception of garlic breath and hair loss, are not really known effects of selenosis. They are probably caused by other things."

Response 4: The paragraph has been replaced. Although selenium has one of the largest published data bases, there are limited studies on selenosis from long term exposure because endemic selenosis is uncommon in human populations. Furthermore, most of the selenosis-related field studies have confounding factors such as malnutrition and smoking. The exact symptoms and mechanisms of selenosis remain incompletely understood.

Comment 5, page 8, line 8: "Inorganic selenium (selenate) is not present in significant amounts in animals."

Response 5: This section has been deleted to shorten the document, so the statement on inorganic selenium in animals has been eliminated.

Comment 6, page 8, mid-page: "The discussion on bioavailability is not helpful. It is merely a list. Moreover, recent work has shown that the bioavailabilities of selenite and selenate in human beings are about half that of selenomethionine (which approaches 100%)."

Response 6: This section has been deleted per reviewers' comments to shorten the document. Bioavailability is discussed in context in the section on selenium absorption beginning on p. 36.

Comment 7, page 11: "Selenium deficiency does not cause Keshan disease. It is a necessary condition for it to occur. Neither is there good evidence that it contributes to HIV-AIDS."

Response 7: This section has been deleted to shorten the document and related discussions on selenium deficiency have been corrected accordingly on pages 66-68. A few papers associating selenium deficiency with AIDS are summarized without further comment on pages 72-73.

Comment 8, page 38, top: "The list of bioavailabilities is bizarre. Less than 10% in milk? Over 100% in nuts? Some critical evaluation of this information is needed."

Response 8: This section has been deleted to shorten the document and related discussions on bioavailabilities have been summarized on pages 21-28, 33-44, and 134-6.

Comment 9, page 91, top: "This discussion of selenium excretion is both simplistic and incorrect."

Response 9: The section on selenium excretion has been updated based on currently available publications on pages 44 to 52 of the document.

Comment 10, page 108, bottom: "The statement about 30 selenoproteins is misleading. There are 25 selenoprotein genes in the human genome. More proteins than this exist because some genes produce isoforms."

Response 10: This section has been deleted to shorten the document and related discussions on selenoproteins have been summarized accordingly on page 58.

Comment 11, page 133: "Much of the material presented in the discussion of selenoproteins is uncritical. An example is the statement that the first selenocysteine of selenoprotein P serves as the active site of an enzyme. This has been postulated but not proven."

Response 11: This section has been greatly condensed and the discussion of the active site of selenoprotein P has been eliminated.

Comment 12, page 141: "This discussion on selenium and diabetes is overly positive. It lacks critical evaluation."

Response 12: This section has been greatly condensed, so the problem related to selenium deficiency and diabetes has been eliminated.

Comment 13, page 152, top: "Selenium deficiency does not usually cause infertility in females."

Response 13: This paragraph has been replaced; we note the existence of some reports of decreased fertility in females on pages 63-64 and 73-74.

Comment 14, page 155, second paragraph: "The statement that selenium may provide benefits aside from its enzymatic functions is misleading. The statement that selenium prevents a number of disorders is wrong. That has not been proven and is totally misleading."

Response 14: This section has been greatly condensed, and the problem regarding interpretation of potential beneficial effects of selenium supplementation has been eliminated.

Comment 15, page 156: "Kashin-Beck disease has not been proven to be caused by selenium deficiency. There is a repeat of this on page 157."

Response 15: The wording has been modified to acknowledge this point, as shown on pages 65 to 66.

Comment 16, page 242: "The statement that "selenite, selenate, and selenomethionine are among the most acutely toxic selenium compounds" obscures the fact that selenomethionine is much less toxic acutely (but not chronically) than the inorganic forms. In fact it is stated on page 292 (correctly) that inorganic selenium has greater immediate toxicity than does inorganic selenium."

Response 16: This discussion has been modified to eliminate the problem, and is now covered on pages 136 and 147.

Comment 17, page 253, last paragraph: "The report of the IOM in 2000 (listed as NRC 2000 here) did not recommend a safe and adequate range of about 50-200 µg/day."

Response 17: This discussion has been replaced as shown on pages 147 to 148 and 155 that the recommendation is based on NAS (1989).

Comment 18: "I recommend that the report be shortened to less than 100 pages long. Critical discussions of the important topics need to be made. Details about the molecular biology of selenium do not need to be included in a report such as this. Helpful sections would be nutritional essentiality, selenoproteins (shortened from what is in this report), metabolism with emphasis on homeostasis (excretion), animal toxicity, human toxicity, selenium exposure (nutritional and toxicological), methods of calculation of PHG, and recommendations."

Response 18: We generally agree, and the resulting document is now only about half as long as the review draft.

Comments from Gerald F. Combs, Jr., Ph.D., USDA

Comment 1: "I would note that I am impressed at both the scope and depth of this document. Its review of the pertinent scientific information about the chemistry, metabolic functions, exposures, cancer-protection, and safety/toxicity of selenium (Se) compounds is thorough and up to date. This is an impressive piece of scholarship that will serve many users and for which your office is to be commended."

Response 1: The kind words are greatly appreciated.

Comment 2: "No sensitive sub population identified - No subpopulation of Californians who might be expected to be notably sensitive to Se has been identified. Therefore, the use of this caution, which affects the mathematical extrapolation of safe levels, is without clear justification. The only highly sensitive individuals that I can think of would be those undernourished with respect to

protein/methionine, or patients with hepatitis – both groups could have compromised abilities to methylate Se and, thus to excrete it. Of course, I am not suggesting that appreciable numbers of Californians may be malnourished, nor that these guidelines should be set for other than healthy people. My point is that I cannot think of healthy individuals whose sensitivity to Se may be different that those studied to data; therefore, I see no reason to use conservative UFs in calculations of safe exposures."

Response 2: We agree that no sensitive subpopulation has been identified based on the currently available publications, and therefore, an uncertainty factor of only three, instead of ten (that is generally used), is used to account for potentially sensitive subgroups including those undernourished with respect to protein and methionine, or patients with hepatitis as shown on page 2.

Comment 3: "Recognition of the IOM UL - 'While the report is complete with respect to the recommendations of the IOM and other national and international agencies regarding, Se requirements and safety, the figure generated by the USEPA as an acceptable daily intake for Se, 350 mcg, is used in the calculations of safe exposure. In fact, the USEPA figure was generated some years before the IOM panel report, and without the benefit of as more recently published data, including global Se intakes and the results of clinical Se-intervention trials. This means that the IOM upper limit (UL) of 400 mcg- Se/day is a much more informed figure. Of course, the IOM figure has been challenged as being too low - Clark's group conducted a trial with some 400 free-living Americans randomized to 0 or 400 mcg supplemental Se/day (total intakes around 500 mcg Se/day), finding no adverse effects (including dermatologic examinations and clinical chemistries conducted at 6 mo. intervals) over 3+ yrs. And normal intakes of healthy people in the Dakotas, Venezuela, and parts of India and China exceed that level. This means that the use of the older, USEPA estimate is not justified. Therefore, I suggest that the safe levels be recalculated using the IOM UL or 400 mcg Se/day."

Response 3: We have discussed the NOAEL of selenium toxicity in detail on pages 139 to 144. In addition, the choice of an appropriate upper consumption limits for adults has been discussed on page 147. Furthermore, we have replaced the alternate subtraction method in the 2006 prerelease draft with a general method for the calculation based on noncarcinogenic effects as shown on pages 145 to 150.

Comment 4: "Inconsistent UFs - I noted that, in various calculations of safe levels, different values were used for uncertainty factors (UFs). For example, in the section on calculations based on non-carcinogenic effects in adults (p. 283), UF values of 2 or 3 are used without clear justification of why different values should be appropriate. Then, in the following section using the Welsh et al. (1981) primary data (p. 284) an UF of 3.5 is used. The apparently arbitrary

selection of UFs gives the impression that calculations were made to achieve pre-determined results or, at least, results in a pre-determined range."

Response 4: The discussions on UFs are on pages 2 and 143 as well as in the calculation on pages 145 to 150.

Comment 5: "Unsubstantiated assumption of the nutritional role of drinking water - It is not self-evident that drinking water should provide no more than 10% of the daily intake of any particular nutrient (other than water). This point should not be considered a given; it needs to be argued on rational grounds. Certainly, drinking water is particularly important in many communities in providing fluoride, and the recent report from the WHO Panel on Nutrient Minerals in Drinking Water shows that the use of moderately "hard" drinking water, which are bound to provide more than 10% of many users' total Mg and/or Ca intakes (these minerals are very widely under-consumed with respect to their RDAs), is associated with reduced risks to ischemic heart disease."

Response 5: This section has been greatly condensed and the problem of the assumption (which basically was just citing WHO guidance) has been eliminated.

Comment 6: "Illogical consideration of Se supplement use - In many of the calculations of safe levels, mention is made of the use of over-the-counter, 200 mcg Se supplements, apparently as implicit justification for the selection of conservative UFs. Basing UFs on this practice is not justified in the absence of sound data on the prevalence of Se supplement use in California. The larger issue is whether water quality guidelines should take into account nutrient supplementation practices that aim, in effect, to increase intakes of the nutrient in question over the normal range of intakes. If so, then the guidelines must accept that the "normal intake" standard does not apply for supplement users, and that the safety of such supplements must be guarded through the regulation of those supplements directly. If the incidence of Se-supplement use in California is low and sporadic, as I suspect, then it would seem unnecessary to consider it in setting water standards of those grounds. In either case, this seems not to be an appropriate consideration for setting water safety standards."

Response 6: This section has been revised and the problem has been eliminated.

Comment 7: "…the draft standards are too conservative and that levels as great as twice those proposed would achieve the goal of protecting public health in California."

Response 7: We have revised the calculation based on consideration of infants. The final PHG of 30 parts per billion (ppb) is slightly higher than the earlier proposed value of 25 ppb.

Comments from Gary E. Olson, Ph.D., Vanderbilt University

Comment 1: "This PHG draft document represents a comprehensive effort to review much of the available scientific literature on selenium and it contains a great deal of useful information. … This effort to assemble such an ambitious document is laudable, and given its extensive bibliography, this document represents a terrific resource for anyone needing information on specific aspects of selenium. As a potential reviewer I was expecting a shorter document, more in line with other PHG documents given as examples, rather than the current draft of ~300 single-spaced pages. Nonetheless the organization of the document into well-defined sections is a strength, because potential readers will be able to readily focus on subsections of interest. However for individuals who read the entire document a weakness of this organization, which also contributes to its length, is that several subsections review the same information (examples below) so that the narrative sometimes becomes repetitive. This repetition might result from different individuals preparing distinct sections of the document, but if it can be eliminated the PHG will be improved, more focused and shortened."

Response 1: The comments are greatly appreciated, and the document has been condensed greatly.

Comment 2: "I'm uncertain of the intended audience for this PHG document. If the target is a nonscientist lay audience then many of the sections which accurately present detailed paragraph-by-paragraph summations of the results of individual published scientific studies will be difficult for them to understand and synthesize into a coherent framework. I think the simplicity and clarity of presentation could be improved…."

Response 2: We have taken many of the specific suggestions in tightening up the data presentation.

Comment 3: "A second general concern to improve readability to the lay audience is that a table including all acronyms and abbreviations used in the PHG should be included very early in the document, I frequently found myself paging back through the document to find the meaning of a particular acronym."

Response 3: We have not included an acronym table to avoid having extra pages in the much shortened document, but hope that the more concise approach will help alleviate the confusion.

Comment 4: "A third general concern for the lay audience was that in discussing separate studies units of measure were not consistent and for example included ug/ml, ug/L, ng, uM/Kg and various other molar units and molar concentrations. I had to do a lot of mathematical conversions to compare different studies being discussed, and if someone is unfamiliar with these units, the task would be impossible."

Response 4: We agree, and have simplified the units used.

Comment 5: "However if the target of the PHG is a scientific audience then a second concern of the present PHG draft emerges. Although numerous studies are briefly discussed, their results are presented as established fact- there appears to be little critical evaluation of the cited studies by the authors of the PHG. Thus even though the draft PHG is an outstanding resource which cites much available literature, readers needing a critical analysis will have to go to the original articles to evaluate their scientific merits. As mentioned above, the inclusion of a summary paragraph for individual PHG sections, which provides a critical analysis of the studies and a discussion of the important concepts, would improve the overall scientific presentation of the draft PHG."

Response 5: We think that the extensive edits in the final document have improved readability for both lay and scientific audiences.

Comment 6: "Finally, because of the wide variety of topics on selenium that are discussed in the PHG, I frequently wondered how all the material related to "selenium in drinking water", the stated focus of the PHG. I urge the PHG authors wherever possible to emphasize the relevance of the diverse topics discussed in this treatise to "selenium in drinking water"."

Response 6: We agree, and have focused on this purpose in the revised document.

Specific Comments:

Comment 7: "I would recommend including a simple diagram on page 8 (last ¶) showing a metabolic pathway for conversion of inorganic to various organic forms of selenium and a table on pg 9 (3rd ¶) that lists the various selenoproteins and their function. I know later in the PHG (table 8) a table of selenoproteins is included but it doesn't discuss their functions."

Response 7: This section has been deleted to shorten the document. The selenium metabolism has been updated on pages 40 to 44 in a much shortened version.

Comment 8: "Pg 10 (2nd ¶) - The molecular biology of selenocysteine biosynthesis is very complex and may not be necessary for most readers. The last sentence is vague, what is the higher "degree of complexity"?"

Response 8: This section has been deleted. Selenoproteins and their functions are summarized in Table 5 on page 58 in a much shortened version.

Comment 9: "Pg 11 (2nd ¶) - The 1st sentence is confusing- why not just say that many selenoproteins play important antioxidant functions?"

Response 9: This section has been greatly condensed and the confusing sentence on antioxidant functions has been eliminated.

Comment 10: "Pg 16 (1st ¶) - There is a big difference in recommended Se intake from the U.S. panel and the commercial supplement industry, which may reflect financial interest of the latter group. This disparity needs a critical comment from the PHG authors because it relates directly to public health."

Response 10: The discussions are shown on page 34 in a shortened version.

Comment 11: "Pg 18 - Is this list of selenium containing compounds important to this document? Overall the section on "Chemical Identities" p16-23 could be shortened without losing impact. I think some of the specific information could be incorporated into tables and this would greatly improve the readability of the text."

Response 11: We agree and this section has been greatly condensed.

Comment 12: "Pg 23 (last ¶) - This paragraph again mentions selenoproteins by name only and lists no function, again a table as suggested for the similar selenoprotein listing in the narrative on Pg 9 would be useful."

Response 12: We agree and this section has been mostly eliminated; the discussion of selenoproteins and their functions is condensed on page 58.

Comment 13: "Pg 26 - The sections on uses and environmental exposure are readable and very informative. After reading about Air, Water and Soil levels (p 27-37) I was wondering about their inter-relationships- do areas with high or low levels in one source, display parallel levels in the other sources? A discussion of the relationship of air and soil Se levels to those of H20 should be included. "

Response 13: The kind comments are greatly appreciated. Discussion of the exchanges among various forms of selenium, i.e., the selenium cycle in the environment, is mainly on page 51.

Comment 14: "Pg 29 (1st & 2nd ¶) - This is an example of where multiple units, e.g pounds, tons, metric tons, ng/m3 are used in rapid succession- maybe just using metric units would simplify the presentation? What is KSp (last ¶) and what is the significance of the number cited?"

Response 14: The units have been made more consistent, mostly changed to grams. This particular section has been deleted to shorten the document.

Comment 15: "Pp 50-54 In these pages much data on Se concentrations of human milk in various populations obtained from many published studies are summarized in a paragraph by paragraph manner. This section ends abruptly and fails to present a big message or concept. This is one example of where the addition of a summary paragraph containing critical analysis and important concepts could be added by PHG staff and would add to the public health significance to the document."

Response 15: This section has been greatly condensed, so the problem has been eliminated; a brief summary of selenium concentrations in human milk and infant formula is on page 29.

Comment 16: "Pg 60 (1st and 2nd ¶) A lot of numerical information is presented in narrative form but it is difficult to assimilate. Maybe it would be more understandable if the data were presented in tabular form and a briefer narrative focused on the important point(s)?"

Response 16: The section on selenium intake has been greatly condensed within pages 29 to 36.

Comment 17: "Pgs 62-72 – This section again essentially represents a narrative list assembled from the published literature of human Se intake by country. This certainly is essential information for establishing recommended Se intake levels but, it is a lot of information to digest and again needs some simplified concluding section. As it currently stands it is a list of published data with no analysis or statements of its relevance to Se in drinking water."

Response 17: The section on selenium intakes has been greatly condensed.

Comment 18: "Pg 72 – I was surprised that this section "intake from water" requires less than one page since it is focus of the PHG? What levels does one find in California?"

Response 18: Information on findings of selenium in water sources in the U.S. has been moved up to the beginning of this section. As discussed in the document, before the recognition of selenium as an essential element in nutrition, selenium was noted for its toxic effects in areas of the world with high soil selenium content. Food is the major source of selenium intake, which is responsible for the observed toxicity. Relative to food, drinking water is a minor source of selenium intake. Intake from drinking water is limited in the U.S. because most of the U.S. drinking water contains very low levels of selenium, as discussed on pages 18 to 21. Specific California data were not found in the available literature, as discussed on pages 33 to 34.

Comment 19: “Pg 72-76 This again represents data from numerous studies on Se uptake from supplements and intake of Se by infants. A critical summation of their importance would be useful.”

Response 19: This section has been greatly condensed; infant intakes are discussed on pages 35 to 36.

Comment 20: “Pp 87-88 - This is a nicely written section on selenocysteine and selenoprotein synthesis but it is somewhat repetitious to information covered earlier e.g. pg 10 and later pg 111-113.”

Response 20: This section has been greatly condensed.

Comment 21: “Pp 110-117 - Will this detailed treatment of selenocysteine and selenoprotein biosynthesis be understood by the target audience? If not, a simplified diagram, citation of appropriate reviews and a simple summary might be adequate?”

Response 21: This section has been eliminated to shorten the document.

Comment 22: “Pg 118 – Table 8 on selenoproteins is useful- can you include a brief statement on their individual functions?”

Response 22: The names and functions of selenoproteins are summarized in Table 5 on page 58.

Comment 23: *The commenter pointed out potential confusion regarding identification of various glutathione peroxidases on pp 119 (last paragraph), 120 (2nd paragraph), and 123 (1st paragraph).*

Response 23: This section has been greatly condensed and the problem has been eliminated.

Comment 24: “Pg 124 1st ¶ - This paragraph does not seem relevant since the protein under discussion is now know to not be a selenoprotein.”

Response 24: This section has been greatly condensed, so the problem has been eliminated.

Comment 25: “Pg 150-152 - This repeats much of the PHGPx (GPx4) discussion on pg 122-124.”

Response 25: This section has been greatly condensed and the problem has been eliminated.

Comment 26: "Pg 152 1st sentence - I don't believe selenium deficiency generally causes infertility in females."

Response: This paragraph has been replaced; we note the existence of some reports of decreased fertility in females on pages 63 to 64.

Comment 27: "Pp 277-291 - I found the section on calculation of PHG to be clearly presented and very thorough presentation of the calculation methods. It will certainly be a valuable resource for individuals interested in the health benefit/toxicological effects of selenium."

Response 27: This section has also been somewhat shortened, but the kind comments are greatly appreciated.

Comment 28: "Pg 300 - The document ends quite abruptly and the addition of a general public health related concluding page and/or policy statements would seem to be a more appropriation ending for this comprehensive document."

Response 28: The general policy statement is in the Preface.

Comments on the 2009 posted draft

Comments from Peter Chapman, Ph.D., Golder Associates, Ltd.

Comment 1: *Dr. Chapman provided a copy of the SETAC Executive Summary document on the Pellston Workshop on Ecological Assessment of Selenium in the Aquatic Environment by Chapman et al. (2009) and a Lawrence and Chapman (2007) publication on consumption of selenium in fish for our consideration for inclusion in the PHG document.*

Response 1: We appreciate the submission. Both of these documents have been reviewed and are now cited in the updated PHG document.

Comment 2: "[C]hildren do not in fact represent a sensitive sub-population; the most sensitive adult population is the adult male."

Response 2: The PHG document does not claim that children are a sensitive subpopulation. The general conclusion as stated in the Introduction is, "data are inadequate to document whether any of these subpopulations are more or less sensitive to selenium toxicity than other groups." A similar statement can be found in the Risk Characterization section. The minimum uncertainty factor of three utilized in the PHG calculation is incorporated to address any aspects of potential human variability that were not present in the populations in China from which the no observed adverse effect level was derived.

Comment 3: “Several of the studies conducted in China used to develop threshold doses of selenium were for primarily vegetarian diets; increased bioavailability of selenium in the Chinese vegetarian diet, among other factors, probably renders the effect threshold values derived from these studies artificially low.”

Response 3: Selenium bioavailability in the endemic selenosis areas in China could be different from the bioavailability of selenium from fish. However, the actual bioavailability of selenium from the varied sources in the diet of Americans with different dietary habits, including vegetarians, is not well documented. For this reason, no adjustment of the estimated health-protective level can be justified.

REFERENCES

Lawrence G S, Chapman PM (2007). Human health risks of selenium-contaminated fish: A case study for risk assessment of essential elements. Hum Ecolog Risk Assess 13:1192–1213.

Chapman PM, Adams WJ, Brooks ML, Delos CG, Luoma SN, Maher WA, Ohlendorf HM, Presser TS, Shaw DP (2009). Ecological assessment of selenium in the aquatic environment. Summary of the SETAC Pellston Workshop on Ecological Assessment of Selenium in the Aquatic Environment, February 2009, Pensacola, FL. Society of Environmental Toxicology and Chemistry (SETAC).