Responses to Major Comments on Technical Support Document

Public Health Goal

For

Water Soluble Polychlorinated Biphenyls Expected to be Found 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 water-soluble polychlorinated biphenyl compounds, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft posted on the OEHHA website. 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 COMMENTS RECEIVED

Comments from University of California, Santa Barbara

Comment 1. "The PHG draft document for Polychlorinated Biphenyls presents the information necessary to develop a Public Health Goal (PHG) for these chemicals. Due to the nature of the commercial mixtures of these chemicals, developing a PHG is relatively complex. In addition, although there have been a significant number of toxicological studies, and a smaller but important number of epidemiological studies, the actual mechanisms of toxicity are not well understood, and the different studies point to different levels of observable toxicological effects. The report presents the available information in a logical manner, and is generally clear in the presentation of the available information."

Response 1: Comments noted.

Comment 2. "Overall, the methodology is correct, and the information used to derive the PHG is appropriate."

Response 2. Comments noted.

Comment 3. "It appears that there is still some concern about posting a numerical value for the PHG, since it is likely to generate some controversy. The value is likely to be significantly lower than the MCL that USEPA has developed for these chemicals. However, it is not hard to calculate the PHG using the equation in Page 45. Thus, it would be better to simply state it and let the discussions begin."

Response 3. The Office of Environmental Health Hazard Assessment (OEHHA) proposes a Public Health Goal (PHG) of 0.00009 mg/L (0.09 μg/L, or 0.09 ppb) for water-soluble polychlorinated biphenyls (PCBs) expected to be found in drinking water. Both public-health protective concentrations for a carcinogenic and non-carcinogenic effect were determined and the most protective concentration was selected. The PHG was obtained using the calculations noted and only after reviewing the relevant studies identified in our literature search, using germane approaches for assessing potential risk from water soluble PCBs.

Comment 4. "The physicochemical data provided in Table 1 is quite useful. However, it is provided as a single deterministic value, when in fact there is a range of values reported in the literature for practically every property. It would be better to provide the range of values, since there is generally no basis for excluding other values."

Response 4. Comment noted. No changes were made since the average value is typically reported for these commercial mixtures.

Comment 5. In Page 5, the analytical methods are discussed. However, there is no mention of specific USEPA methods of analysis, or typical practical quantitation limits in commercial laboratories. Since it is quite probable that the PHG will be set below the practical quantitation limit, this will be a critical point in the discussion. I would strongly recommend that this section be expanded and supported with results from lab comparison studies using state-of-the-art analytical instruments and methods."

Response 5. Appropriate references were included in this section that would provide the reader with detailed data regarding the analytical quantitation limits and methodology. However, the purpose of PHG documents is to summarize the health-effects information. Analytical and economic considerations are the responsibility of the Department of Health Services, in developing the Maximum Contaminant Level (MCL).

Comment 6. "Although the report presents some typical concentrations in some environmental media, it would be useful to provide more specific data on air, water, sediment and fish tissue."

Response 6. Available data are included in these documents for perspective and estimation of a relative source contribution of a chemical in drinking water, and the data provided appear to be adequate for this limited purpose. A full discussion of the environmental distribution of pollutants is outside the scope of these documents. Therefore, no changes were made in response to this comment.

Comment 7. "In some cases (e.g., last paragraph in Page 12), an exception is mentioned, but no values are associated with the exception, leading the reader to wonder what this means."

Response 7. Document was revised accordingly.

Comment 8. "In Page 17, the first paragraph related to subchronic toxicity refers to histological changes observed at doses 'less than 100 mg/kg'. It would be better to present a range, since clearly the lower value is not 0 mg/kg."

Response 8. Revised to state "less than 10 mg/kg," but otherwise left as before, which goes on to refer to Table 2 for the actual range of values.

Comment 9. "In Page 23, a number of studies are cited, but no dose is mentioned, which makes it difficult to know whether these studies are relevant, and whether these effects would be seen at the PHG or not."

Response 9. Doses are now provided for the studies that did not have them originally.

Comment 10. "For the non-carcinogenic effects, four different concentrations are calculated, based on different health effects (developmental/neurological, developmental/immunological, developmental/low birth weight, reproductive). That part

is fine, but it makes no sense then to calculate the geometric mean of these concentrations. It makes more sense to use the lowest value as the desirable goal (around 0.1 ug/L), since we clearly do not want to have a higher risk for one effect than the target risk level. The point becomes moot if one uses the carcinogenic effects level for the PHG, but then what is the point of the geometric mean? I would not go through that discussion."

Response 10. The differences in these calculations involved professional judgment as to appropriate uncertainty factors for various effects in the same two studies. The effects occurred at basically the same treatment levels, so this was not a matter of increased toxicity deserving a more health-protective (lower) level, or any quantifiable higher risk of one effect versus another. The discussion of the rationale for a geometric mean has been clarified and is included in the document for completeness.

Comment 11. "However, not every study was reviewed to guarantee that all the data is accurate and that there have been no important omissions."

Response 11. An extensive literature search was made in order to identify all relevant studies, and those that are useful for our purposes – to estimate a health-protective level in drinking water - have been cited and described. The PCB literature is quite extensive, and many very good PCB studies, particularly relating to environmental distribution and effects, have not been cited. The reader is directed to other reviews on these more general aspects.

Comment 12. "In Page 28-32, a number of epidemiological studies are mentioned, but there is no discussion of the estimated dose(s). Clearly it is difficult to determine an exact dose, but at least some estimate should be made, to put these studies in context."

Response 12. Although information exists about the adverse effects of PCBs in humans, clear direct evidence is lacking as well as a certainty about the doses at which these effects were seen. However, these studies evaluated PCB exposure following food consumption (e.g., fish or contaminated oil). The purpose of this document is to establish a public-health protective concentration of water soluble PCBs in drinking water. Thus the extent of which these studies are used in our document is to demonstrate the evidence that PCBs may be carcinogenic in humans. Even with the limitations of these studies (i.e., lack of good dose information, preventing establishment of a direct correlation between effect and PCB exposure; inconsistent results; difficulty interpreting co-exposure to other potential carcinogens; limited exposure information; and the small samples sizes in most epidemiological studies), these studies do provide some evidence that PCBs are carcinogenic in humans, including the more water-soluble PCBs. In addition, the trends of effects that are reported in the human studies are corroborated in many cases by the animal studies.

Comment 13. "The approach used to develop the PHG follows established USEPA guidelines. This is a complex set of chemicals, both due to the fact that the actual mixture of congeners varies with formulation and with time, and the differential

physicochemical and physiological response for each congener and within the commercial mixture. Thus, a major issue is determining which set of congeners to use as the basis for the PHG. The approach used in this case, based on the most soluble congeners, makes sense given that this is a drinking water PHG. With regards to the factors determined by USEPA, one can question the methodology used by USEPA, but at least the PHG is consistent with the previous work. The cancer slope factor used (0.4 mg/kg-d) seems appropriate for a drinking water PHG since it is based on the more likely mixture of congeners that are likely to be present in these water supplies, although once could argue that the Aroclor 1016 mixture is also applicable for drinking water considerations, which would result in the use of a much lower CSF (0.07 mg/kg-d)."

Response 13. Aroclor 1016 was also considered part of the water-soluble congeners. However, the higher CSF was used in our calculation because it is the more health-protective value.

Comment 14. "Within the document, there is no critical evaluation of the method used by USEPA to determine the cancer slope factors (CSF) based on the available data. The reader must assume that OEHHA staff agrees completely with the determination of the CSFs. There is room for discussion with regards to the selection of the upper bound CSF for the 'low risk and persistence tier', given that the range of values is from 0.08 to 0.4 mg/k-d, yet the selected value is 0.4 mg/kg-d. The document should provide justification for this choice of CSF."

Response 14. OEHHA is in agreement with the determination of the US EPA's three-tiered approach for PCBs, and the choice of the upper potency value in the mid-tier range used for this risk assessment. The value of 0.4 mg/kg-day for cancer potency in females, versus the values of 0.1 and 0.08 in male rats seemed likely to represent a true sex-specific potency difference. This rationale for accepting the higher value recommended by US EPA has been added to the discussion.

Comment 15. "A number of key studies are identified in the Draft PHG document. Since there is no specific 'conclusion', i.e. a numerical value for the PHG is not defined within the document, it is difficult to state that the data supports the conclusions. It appears that the PHG will be set based on the carcinogenic effect, at a level slightly below 0.1 ug/L, which is below the stated practical quantitation limit (0.5 ug/L). This will generate considerable discussion among the stakeholders. There is insufficient data in the document to support the statement that the practical quantitation limit (PQL) is 0.5 ug/L; more information should be obtained to confirm this value, or better yet to determine the state-of-the-art PQL."

Response 15. OEHHA is proposing in this document a Public Health Goal (PHG) of 0.00009 mg/L (0.09 μg/L, or 0.09 ppb) for water-soluble polychlorinated biphenyls (PCBs) expected to be found in drinking water. A PHG is based exclusively on public health considerations without regard to cost impacts or technical feasibility. PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels,

or MCLs). Whereas PHGs are used solely on scientific and public health considerations without regard to economic cost considerations and technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility, including the practical quantitation limit (the "Detection Limit for the Purposes of Reporting; as described in: http://www.dhs.ca.gov/ps/ddwem/chemicals/monitoring/detectionlimitsdefinition.pdf). California law also requires that the standards adopted by DHS shall be set at a level that is as close as feasible to the corresponding PHG (see http://www.dhs.ca.gov/ps/ddwem/chemicals/MCL/process.htm).

Comment 16. "Appropriateness of risk assessment methodology – The CSF used to establish the PHG is essentially based on two studies, Mayes et al. (1998) and Schaeffer et al. (1984, since these are the ones that correspond to the 'low risk and persistence tier'. The studies are reasonable well summarized in the Draft PHG, although additional information n on the number of test animals and incidence of effects for the Schaeffer study could be included to provide a more complete picture. There are two important concerns with regards to the methodology: (1) the number of studies upon which the actual PHG decision is based is quite limited; (2) the studies are somewhat date, particularly the Schaeffer study. Ideally, one would conduct new studies, following state-of-the-art methods, and with sufficient reproducibility to be sure that the results are accurate. The cost of compliance by the eventual regulated community (suppliers of drinking water) may or may not justify these newer studies; it is beyond the scope of this review to assess whether this is the case. Given that 'of the 4,985 drinking water sources analyzed for PCBs in California from 1984 to 2001, none had reportable PCB levels (DHS, 2002)', it does not seem like new studies are warranted."

Response 16. Although OEHHA concurs with the commenter that new studies may not be warranted, such decisions are beyond the scope of the PHG process.

Comment 17. "The calculation of the PHG is based on a 70 kg person, but this is a very high weight for females. The PHG should be based on a more likely weight for females, rather than the 'average' male. In fact, most males are likely to weight more than 70 kg in the US. A lower weight would result in a more conservative PHG".

Response 17. The use of a 70-kg body weight in the calculation of the PHG is a standard default for cancer risk assessment, and in some evaluations has been found to be close to the 50th percentile value of the combined distribution of adult male and female body weights (see pg. 10-2, Air Toxics "Hot Spots" Program Risk Assessment Guidelines Part IV, Sept. 2000). We acknowledge that average weight over a lifetime will differ from this default. Recent efforts at OEHHA and U.S. EPA to consider variations in exposure over a lifetime on a bodyweight x time-adjusted basis may result in recommendations for changes in this and other defaults.

Comment 18. "The most likely exposure is through food. The document makes this clear. However, the PHG focuses on drinking water, since that is the objective.

However, from a public health perspective, it would be useful to establish acceptable levels of PCBs in commonly available foods (e.g. fish, seafood, dairy, etc.). Although it is beyond the scope of the current PHG document, it would be important to do so in a different document, and to mention this in the document."

Response 18. Comment noted. OEHHA is also working on health advisories for chemicals in fish, but not, at this time, in other foods.

Comment 19. "The calculations presented are deterministic, with no mention or discussion of the underlying uncertainties. The largest uncertainty in the calculation is associated with the CSF. The values used in the 'low risk and persistence tier' vary over a significant range (0.08 to 0.4 mg/kg-d). It would thus be appropriate to consider the range in the calculation, and a justification of the use of the higher end should be provided. In addition, the small number of studies used for determining the CSF introduces additional uncertainty. More discussion is needed in this regard within the document. One needs to convey to the public that the fact that the PHG is a conservative value (i.e. quite protective), but that there is uncertainty in its calculation."

Response 19. Comment noted. Document was revised accordingly.

Comment 20. *Several editorial comments were provided.*

Response 20. Changes were made to the document, where appropriate.

Comments from University of California, Davis (reviewer 1)

Comment 1. "In general, the document is very well written and thorough. The data used appear to be both reliable and generally defensible. Rationale is clearly stated, thus the report also supports its conclusions and recommendations."

Response. Comment noted.

Comment 2. "The information presented is quite thorough and complete [on toxicity, toxicokinetics, metabolism, mode(s) of action and exposure]. In fact, the introductory sections represent a nice review paper that could easily be a candidate for peer-reviewed publication."

Response 2. Comment noted.

Comment 3. "One minor point [on the Metabolism section]: the reference to Safe (1980) on page 11 and elsewhere is quite old, and the full citation is not included in the References section. Is there not a more timely review of PCB metabolism available?"

Response 3. References provided in these sections provide specific citations to emphasize a particular point. For a general overview of the metabolism of PCBs, the

reader is referred to a more recent publication [ATSDR. Toxicological profile for polychlorinated biphenyls. Agency for Toxic Substances and Disease Registry, Division of Toxicology, Atlanta, Georgia (2000)]. The document was revised accordingly.

Comment 4. "The data sets representing both carcinogenic and non-carcinogenic effects of PCBs are relatively complete in terms of representing the information currently available. They also appear appropriate in terms of the test species and PCBs used. The mechanistic data more than adequately represents what is currently available in the scientific literature."

Response 4. Comment noted.

Comment 5. "The data clearly support the conclusions, and the dose-response assessment approach appears to be adequate (e.g. the use of oral studies to assess non-carcinogenic human risk from drinking water)."

Response 5. Comment noted.

Comment 6. "A couple of key concerns. First, are the carcinogenic effects studies based on oral exposures? While I assume this to be the case (as alluded to on page 36), it does not appear to be obvious from the related tables or text. Second, the risk focus appears to be on oral consumption of drinking water by humans (see reference to the EPA on the bottom of page 40). However, it is stated in the introductory sections (correctly) that PCBs volatilize from water (due to poor water solubility) and can be absorbed across the skin (due to high fat solubility). Were either of these exposure routes also considered, particularly when humans may be showering daily in warm-to-hot water? It is not clearly stated in the document as to why other routes were not included in the PHG." "However, if other routes of exposure are deemed insignificant…, please more clearly state the rationale in the document (i.e. summarize the rationale presented in EPA 1996b)."

Response 6. Comment noted. Document was revised accordingly. When determining cancer and non-cancer public-health protective concentration using the appropriate cancer slope and the relative source contribution, respectively, both inhalation and dermal routes (as they relate to tap water exposure) are indirectly considered in these two parameters.

Comment 7. "Other than the limited focus on oral consumption of PCBs, the methods [for risk assessment] appear to be appropriate."

Response 7. Comment noted.

Comment 8. "The proposed PHG of 0.09 ppb, which is inclusive of both cancer (0.09 ppb) and non-cancer (0.3 ppb) endpoints, appears appropriate for oral consumption, and the rationale is clearly stated."

Response 8. Comment noted.

Comment 9. "The uncertainties in the PHG are appropriately identified and quantified. The conclusion provides adequate public health protection for oral consumption of PCB-containing drinking water."

Response 9. Comment noted.

Comments from University of California, Davis (reviewer 2)

Comment 1. "In many respects, this document is well-written, and well-researched. It was clearly a challenge to develop a rational strategy for assessment of risks from a rather minor source (as compared with food) of PCB exposures. The background information on production, chemical properties, sources of exposure, distribution in the body, metabolism & excretion is informative and appears to be accurate."

Response 1. Comments noted.

Comment 2. "The emphasis on the Ah-receptor has historical roots, but the wide array of mechanisms supported by the literature would argue for presentation of the many non-Ah receptor-mediated mechanisms in considerably greater detail. For example, the body of work describing several discrete pathways by which disruption of thyroid hormone homeostasis takes place (interference with elimination, binding to carrier proteins, etc.) deserves a more complete discussion, especially as this mechanisms underlies altered neurodevelopment, and thyroxine replacement is shown to attenuate these effects in rodents."

Response 2. Yes, the biological effects observed following administration of different PCB mixtures differ qualitatively and quantitatively and suggest the possible existence of multiple and diverse mechanisms. Since a clear understanding of the toxic mechanism(s) of PCBs is not yet available, we elected to briefly review the key postulated mechanisms in this document. A more detailed discussion is unnecessary for purposes of this risk assessment.

Comment 3. "The review of the epidemiologic literature on carcinogenicity omits a very large group of studies on breast cancer, the vast majority of which showed null results. Several meta-analyses of these studies have been published, also reaching the conclusion of no association."

Response 3. Yes. The breast cancer potential was omitted because results showed no association between PCB exposure and breast cancer. However, because of the perspective this large body of data provides on the carcinogenic potential of PCBs, a brief discussion on the breast cancer studies has been added to the human carcinogenicity section.

Comment 4. "Some few key studies from the toxicologic literature appeared to have been omitted, such as the cross-fostering experiment by Goldey and colleagues showing pre- as opposed to post-natal exposures having the strongest effect on hearing loss, and emphasizing hearing loss as a particularly sensitive endpoint."

Response 4. Several additional studies were reviewed and are now described in the Neurotoxicity section.

Comment 5. "There are two aspects to the approach taken for calculation of Public Health Goals (PHGs) that are of concern. First, the developmental outcomes observed are the result of short-term exposures (e.g., during pregnancy, or possibly from pregnancy through weaning): it was not clear how this was taken into account in the derivation of the PHGs for developmental outcomes, and how the inter-species conversion should be done for the longer gestation in humans as compared with rodents."

Response 5. OEHHA assumes that 10-fold interspecies uncertainty factor is adequate to extrapolate from the most sensitive animal species tested to human effects for reproductive endpoints. Use of this factor should account for the difference in duration of the gestational exposures. Since there are primate data in this case (for relevant neurobehavioral endpoints), we feel confident that the extrapolation procedures used should account for the potential species differences. However, the PHG is based on the cancer potency, which provides an even lower value. Therefore we feel that the PHG will be adequately protective against the developmental effects of PCBs.

Comment 6. "Secondly, the averaging of PHGs derived from several developmental outcomes and then comparing to the PHG based on cancer seems to be thoroughly arbitrary and lacking in scientific basis. Either all should be averaged (cancer and non-cancer), or the lowest of the non-cancer should be compared with the cancer, or the lowest of the four should be adopted outright. In other words, whether it changes the ultimate PHG recommended for water-soluble PCBs or not, the approach should be based on a coherent algorithm, which the current document lacks. Moreover, as any given individual could be susceptible to all endpoints, averaging PHGs seems problematic in the first place. While the final result would appear to be the same in this case, in other instances, it might not be."

Response 6. The approach used at OEHHA is to derive the most sensitive public health-protective concentration for a carcinogenicity or non-cancer outcome, using the latest regulatory models and most viable assumptions. The most sensitive of the two is designated as the PHG. When there are a lot of data with variable apparent potencies, OEHHA has, in the past, chosen to apply a geometric mean of what appear to be the more relevant or most sensitive studies (e.g., the arsenic PHG). The rationale for this is usually that the different quantitative values may represent a random distribution of results. This thinking would not necessarily apply for cancer versus non cancer endpoints, so it does not seem appropriate to combine these data in that way.

Evaluation of the non-cancer effects of PCBs was complicated by the variability in the mixtures to which people might be exposed, as well as the wide variety of potential toxic effects. Considering the different strengths and weaknesses of the studies cited in the document, varying potencies, possible varying - and even opposing - mechanisms of action, and distribution factors, the most relevant effect was not clear. However, because the effects occurred at basically the same treatment levels, this was not a matter of increased toxicity deserving a more health-protective (lower) level, or any quantifiable higher risk of one effect versus another.

Comment 7. "A further issue is the severity of the endpoint: for instance, is low birth weight or a change in a single immune parameter comparable to cognitive developmental delay in a child, or cancer in a 75-year old? While this document may not be the place to develop a coherent approach for dealing with very disparate outcomes, some comment on altered immune parameters vs. clinical outcomes of consequence may be in order."

Response 7. We acknowledge the difficulty in making such decisions or distinctions among effects and populations in risk assessment. OEHHA is committed to protecting against all adverse effects in identifiable subpopulations, and feel that in using the most sensitive endpoint for deriving the PHG, the PHG level in this case is fully protective of all endpoints (without the necessity for considering one type of toxicity more or less important than another).

Comment 8. "p. v., top paragraph, sentence "Non-occupational exposure to PCBs…" should also mention that a primary source for infants is breast milk."

Response 8. Agreed; the document was revised accordingly.

Comment 9. "p. v., paragraph "A public health-protective…" uses the terminology 'neurological' when the effects referred to concern neurobehavioral development. The two terms generally refer to very different endpoints…tests of neurologic damage include reaction times, reflexes, etc., and apply to all ages, including adults. Neurobehavioral development includes outcomes related to acquisition of cognitive skills, learning, and adaptive behaviors during early life, and signifies the degree to which the organism achieves or can achieve his/her potential. Most of the literature on PCBs is based on the latter in relation to both prenatal and postnatal exposures."

Response 9. The entire document was revised to reflect a clarification of the term "neurological effects" when the effects referred to concern neurobehavioral development.

Comment 10. "p.1, 2nd paragraph, sentence "A geometric mean…": it is unclear at this point whether the geometric mean was calculated across endpoints or only across studies within an endpoint."

Response 10. Across endpoints; this section of the document was revised for clarification

Comment 11. "Later it becomes clear that this is across endpoints, which raises concerns, since the same individuals could be vulnerable to all of the endpoints, and thus, the effects could be additive, with no additional dosing. The aim should be to derive a health-protective dose, which will not be achieved by averaging across endpoints. There is no statistical or scientific or public health justification for averaging estimated safe doses."

Response 11. This is addressed in the response to comment 6. It should additionally be noted that the question of "vulnerability to all the endpoints" is true in each of the animal studies, and in each study, the most sensitive endpoint was used for the calculation.

Comment 12. "p. 2, final paragraph, sentence "A cancer potency estimate of 2…" has the awkward phrase "for high risk and persistence conditions…" A suggested rewording might be "for high risk and highly persistent conditions."

Response 12. The terms "high risk" and "persistence" correspond to the classification terms used in the U.S. EPA guidance document for selecting corresponding carcinogenic slope factors. The statements were revised for clarification, to reflect the corresponding tier levels.

Comment 13. "p. 8, 2nd paragraph: there are two statements about intake, and the link between them needs to be made. "Adult dietary intake during 1982-1984 was estimated as 35 ng/day (ATSDR, 1996)." This is followed by the sentence "The estimated dietary intake of PCBs for an adult was 0.27 ug/kg-day in 1978 and 0.0005 ug/kg-day in 1982-1984 (ATSDR, 1996)." It should be made explicit that one of these calculations was based on the other, using a 70 kg person."

Response 13. Document was revised accordingly.

Comment 14. "p. 8, 3rd paragraph: the report points out that some persons who consume sport-fish may be ingesting vastly higher quantities of PCBs from food, e.g., resulting in exposures that could be as much as 500 times higher than the average of 35 ng/day. If the dose-response is not linear-additive, then the impact from water consumption could be higher or lower than what is estimated. Suggestions of steeper dose-response curves at lower exposures have been noted in the literature on environmental chemicals and certain reproductive or neurobehavioral outcomes. In what way was this scenario figured into the calculations of the PHG? The population that regularly consumes fish from the San Francisco Bay is comprised primarily of the poor and of immigrants. Many are young families. This population may be at exceedingly high risk of adverse health effects, and the impact of water consumption could be disproportional. These concerns should be addressed."

Response 14. The objective of this document is to derive a public health-protective concentration for water-soluble PCBs in drinking water. Available data (i.e., presence of PCBs in other media) are included in this document for perspective and estimation of the average relative source contribution of a chemical in drinking water. We acknowledge

that high consumers of sport fish are a population of concern for consumption of PCBs, and OEHHA is also working on health advisories for chemicals in sport fish. However, the data are insufficient to evaluate the possibility of a non-linear (supra-additive) dose-response for non-cancer effects of PHGs. Development of the PHG based on the cancer potency models, with a lower resulting value, should help protect against such unknown and non-quantifiable potential effects and interactions.

Comment 15. "p.13. A glaring omission in the first paragraph under "Mechanism of Action," in reference to non-Ah-receptor mediated mechanisms are the several avenues leading to disruption of thyroid hormone homeostasis."

Response 15. OEHHA has acknowledged non-Ah-receptor mediated effects in the revised document. Toxic effects observed following the administration of different PCB mixtures vary qualitatively and quantitatively and suggest the possibility of multiple and diverse mechanisms. Since a clear understanding of the toxic mechanism(s) of PCBs is not yet available, we elected to briefly review the key postulated mechanisms in this document, but did not choose to discuss in detail the possible mechanisms of thyroid hormone disruption.

Comment 16. "p. 23: Earlier work out of Crofton's lab showed auditory effects at 1 mg/kg/day that were long-lasting (Herr et al. 1996). The auditory effects were considered among the most sensitive of developmental endpoints. Outer hair cell development in the cochlea appeared to be the mechanism, which translates to a prenatal developmental period in humans. It would be helpful to provide doses for Crofton et al 2000, and Gilbert et al 2000."

Response 16. Agreed; doses can be found within the text of the corresponding section.

Comment 17. "p. 24, last two paragraphs: Is it correct that Arnold et al. 1995 observed the same four outcomes as Tryphonas et al. 1989, and 1991 – tarsal gland inflammation, nail lesions, gum recession, and reduced IgM antibody levels to SBRC? If these are three different reports from the same study then they should at least be condensed into the same paragraph, and it should be clarified how many different studies they were and how the dosing or other aspects of the study differed. Note that in the last paragraph, these are referred to as immunological, whereas in the previous paragraph they are referred to as "developmental." Also, the last paragraph refers to an exposure of up to 55 months, whereas the previous paragraph does not specify either the length of exposure or the length of follow-up."

Response 17. Arnold *et al*. and Tryphonas *et al*. published a series of articles at different stages of the one monkey study, with Arnold *et al.* concentrating on reproductive and infant effects and Tryphonas *et al*. on the immunotoxic effects in adults. The paragraphs were not condensed in order to highlight the two types of endpoints evaluated in the different reports. However, the wording has been clarified, with doses and treatment periods specified more clearly.

Comment 18. "p. 29, second para: A finding of increased circulatory disease mortality risk is *highly* unusual in an occupational study, largely because of the healthy worker effect, which is associated with reduced mortality from cardiovascular conditions; for this reason, the finding deserves serious consideration. The fact that other studies did not observe this outcome could easily be due to lower exposure, shorter latency, or a host of other deficiencies. In reviewing epidemiologic studies, it is important to weigh the high quality studies more heavily than those which lack basic requisites. Here and elsewhere in the document, there is no attempt to distinguish strong from weak epidemiologic studies. If the inconsistency is from some studies being poorly conducted, there is no reason to dismiss evidence from strong studies."

Response 18. We have attempted to include the most appropriate studies in the discussion, and extensive revisions in wording were made for increased clarity. We agree that the epidemiological studies evaluating the possible association between PCB exposure and various effects including circulatory disease provide important perspectives on PCB hazards, which should not be dismissed. However, the studies have several methodological limitations which preclude their use in calculating health-protective levels of PCBs in drinking water.

Comment 19. "p. 30, 2nd para: The sentence "In the review by…" implies that there were 39 occupational studies that examined developmental effects. This seems highly unlikely. Secondly, one can't necessarily compare reproductive effects, which are quite variable. Thus, any attempt to count up the beans for reproductive effects is nonsense. One must discuss low birth weight separately from male infertility separately from female infertility, separately from menstrual irregularities separately from preterm delivery separately from spontaneous abortion, etc. There is actually a fairly consistent literature, when examining higher quality studies, with low birth weight, for instance. The statement "The lack of consistency was reported to reflect the differences in controlling for confounders and/or the different exposure measures, levels, and substances" seems to confuse several issues. If strong studies show an association and studies that fail to control for confounders or have other major deficiencies do not, then the evidence is not weak; on the contrary, this pattern may be exactly what one would expect if the agent were causally related to the outcome. Not only is 'consistency' not required for evidence to be strong, 'inconsistency' is to be expected when exposures differ either qualitatively or quantitatively. The Swanson paper was 10 years old at the time this document was prepared, but if they indeed reported no environmental exposure studies showing positive or suggestive findings, it seems they may have missed a few (e.g., Fein). More importantly, quite a few papers have appeared since then. Studies from the Netherlands, the Inuits, and elsewhere provide a stronger case than the PHG document suggests. Additionally, several newer papers on perinatal effects were published in the year since this document was assembled."

Response 19. Several revisions were made to this section in order to clarify current status of the various types of developmental effects observed with environmental exposure to PCBs.

Comment 20. "p. 31: The first paragraph mentions most of the older studies on cognitive and behavioral development. The second paragraph asserts that there were limitations in these studies. How serious were the limitations? What was the likely net effect of those limitations, in terms of bias and precision? Similar to the section on "Reproductive and Developmental Toxicity," the document appears to dismiss a sizable literature of reasonably strong quality, without good cause. The document under-rates the quality of several of the cited studies. Neurodevelopmental toxicity in human populations with exposures at relatively low levels mirrors the findings in animal studies, as well as those in high-exposure accidents, and many of these studies adjusted for a wide range of confounding factors and/or used exposure indices of good quality. The evaluation of the evidence here is not well-justified."

Response 20. The document was revised to add some of the studies reviewed, but not included earlier. Since exposure levels cannot be determined in the human studies in question, they are inherently "weak" from our perspective, and cannot be used to determine the public health-protective concentration for water soluble PCBs found in drinking water, irrespective of their other strengths. Thus, these studies were only briefly summarized.

Comment 21. "The argument that because PCBs are accompanied by contaminants deserves further consideration. If PCBs are accompanied by dioxins and furans in virtually all human exposure scenarios, then one cannot dismiss these exposure scenarios; risk assessments for PCBs need to be realistic. Moreover, the mechanisms associated with PCDDs resemble those of PCBs, again suggesting that studies of human populations exposed to these mixes are highly relevant. This would be similar to regulations related to environmental tobacco smoke, where the exact constituents are not fully and completely characterized, and may vary from one location to another, from one cigarette brand to another, etc., but still provide a coherent body of evidence and are regulated as a group of compounds.

Response 21. We concur that the contaminants can be biologically relevant and the PCBs do need to be considered as part of any pertinent groups (e.g., water soluble PCBs, co-planar PCBs). However, the drinking water milieu limits some of the more toxic contaminants and potential interactions compared, for example, to the mixtures found in fish. The purpose of this risk assessment is to develop a PHG for the more water-soluble PCBs, and corresponding data on the lower-chlorinated dioxins and furans are not readily available. Therefore, whereas we agree that there is a potential for interactions of such contaminants with the PCBs, the potential mechanisms and effects are not well established (i.e., additive, synergistic or inhibitory). Thus our risk assessment is based on the most relevant outcomes and potency tier estimates that are available.

Comment 22. "[p. 32] Third paragraph, last sentence: "but have not been clinically revealed" is unclear. Does this mean that the self-reported symptoms were not

confirmed? Or does it mean that despite the symptoms, tests of other endpoints did not show clear evidence of functional nerve damage? How strong were these studies?"

Response 22. The sentence was clarified to state that the self-reported symptoms "have not been clinically confirmed."

Comment 23. "p. 41: the argument against using TEF's is reasonable if the outcomes are considered to be the result of non-Ah receptor mediated mechanisms. It's not clear whether the endpoints chosen fall into this category, esp the cancer potency used to derive the final PHG recommendation."

Response 23. We agree that cancer may be mediated through an Ah-receptor mechanism, but the substance of the argument was, first, that not all water-soluble PCBs should be assumed to work through Ah-receptor mechanisms, and, second, PCBs are monitored as a group in drinking water, not via TEF-equivalents. Therefore using the TEF approach in recommending a PHG level as the basis for our risk assessment did not seem appropriate.

Comment 24. "p. 42: is it customary to consider monkeys to be as distant from humans as rodents are, in terms of inter-species extrapolation factors? This seems problematic."

Response 24. While monkeys are certainly more similar to humans than rats, there are no well-accepted uncertainty factors for extrapolations from each of the common experimental species to humans. The approach taken by OEHHA is to use a factor of 10 for all inter-species extrapolations unless there is specific information relevant to that chemical and species supporting a different approach.