OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Goal

Responses to Peer Review and Major Public Comments on Technical Support Document

Public Health Goal for Antimony in Drinking Water

September 2016

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

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Office of Environmental Health Hazard Assessment
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INTRODUCTION

This document contains responses to peer review and major public comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on drafts of the public health goal (PHG) technical support document for antimony.

OEHHA released a draft of this PHG document for public comment on July 23, 2009. The public comment period closed on October 13, 2009, after a 30-day extension. OEHHA received comments from the International Antimony Association, Kent State University, and the PET Stakeholders Ad Hoc Issues Coalition. The document was subsequently revised in response to these comments.

Pursuant to Health and Safety Code Section 116365(c)(3)(D), the revised draft PHG underwent external scientific peer review using the process set forth in Health and Safety Code Section 57004. The University of California, pursuant to its interagency agreement with CalEPA regarding external scientific peer review of documents produced by CalEPA programs, identified the three peer reviewers of the draft document. OEHHA received the peer reviews in February 2016.

The three peer reviewers were:

- Jay Goodman, Ph.D., Professor, Department of Pharmacology and Toxicology, Michigan State University
- John Pierce Wise, Sr. Ph.D., Professor of Pharmacology and Toxicology, University Scholar, University of Louisville
- Stephen Nesnow, Ph.D., Director, Stephen Nesnow Consulting, Chapel Hill, NC.

After taking into consideration reviewer comments, OEHHA released the next draft PHG document for public comment on July 22, 2016. The public comment period closed on August 22, 2016. OEHHA received comments from the U.S. Department of Defense.

Changes to the PHG document have been made in response to these comments. Thus, the final version of the PHG document posted on the OEHHA web site takes into account all public and peer reviewer comments.

For the sake of brevity, the more important or representative comments were selected for responses in this response to comment document. Comments appear in quotation marks where they are directly quoted from the submission.

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, FIRST COMMENT PERIOD (SEPTEMBER 2009)

Comments from International Antimony Association (i2a), Brussels, Belgium

General Comment: "As a general point, the OEHHA draft does not appear to recognise that a detailed EU Risk Assessment Report (RAR) on diantimony trioxide was recently finalised and published; this was subsequently discussed and endorsed at OECD level in 2008."

Response: The European Union (EU) RAR on Diantimony Trioxide was identified and available to OEHHA only after the development of the draft PHG document. OEHHA has since reviewed it and included relevant information in the PHG document.

Comment 1: "Industry is wondering why the authors did not use an adult water consumption of 2 L/day like in the OEHHA 1997 version on antimony in drinking water. Two litres per person per day has been used as the default value for water ingestion by EPA, other Federal agencies, and the WHO [World Health Organization]."

Response 1: OEHHA develops PHGs using the most current principles, practices, and methods used by public health professionals. As such, OEHHA is replacing the outdated default adult water ingestion rate of 2 L/day with age-specific water ingestion estimates (OEHHA, 2012) derived from a nationwide survey of food and beverage intake from approximately 20,000 individuals (United States Department of Agriculture's Continuing Survey of Food Intake of Individuals (CSFII) 1994-1996, 1998 dataset). These age-specific intake rates are normalized to body weight and expressed as liters of water ingested per kilogram of body weight per day (L/kg-day). The US Environmental Protection Agency (US EPA) has also developed recommended drinking water ingestion rates based on the same CSFII dataset, as well as the 2003-2006 data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey, for use in exposure assessment (US EPA, 2011). OEHHA currently uses the time-weighted lifetime average drinking water consumption rate for the general population calculated from lifestage-specific water consumption rates. Specifically, for an average lifespan of seventy years, OEHHA uses a water consumption rate of 0.196 L/kg-day for the first two years of life, 0.061 L/kg-day for the next 14 years, and 0.045 L/kg-day for the remaining 54 years, and the time-weighed lifetime average drinking water consumption rate of 0.053 L/kg-day can be derived based on the following calculation:

consumption rate = (2/70*0.196+14/70*0.061+54/70*0.045) L/kg-day

= 0.053 L/kg-day.

Comment 2: i2a notes the apparent contradiction between two statements in the document. In one sentence, it appeared that OEHHA acknowledged pentavalent antimonials were important medications in the treatment of leishmaniasis, whereas in another instance OEHHA suggested that they were being phased out for this condition.

Response 2: Pentavalent antimonials are still key agents used to combat leishmaniasis, but it is unclear whether they will continue to play a significant role in the future, due to development of resistance of the parasite to the antimonials (Croft et al., 2006). These statements have been clarified.

Comment 3: i2a suggests that the deposition of antimony in the environment is complex, related to both natural and anthropogenic processes, and recommends that OEHHA consider the information presented by Reimann et al. (2010).

Response 3: OEHHA agrees, and has cited the recent review by Reimann et al. (2010) in revising this paragraph.

Comment 4: "The context and the citation [ATSDR, 1992] given in the document lead to wrong conclusions. … Occupational exposure values from that time [Donaldson, 1976 as cited in ATSDR 1992] are not considered to reflect current occupational hygiene practices. A more recent compilation of occupational exposure data is provided in the EU-RAR on diantimony trioxide."

Response 4: Occupational exposure occurs primarily through the inhalation and dermal routes and from media other than drinking water. Therefore, the discussion on occupational exposure is now removed from the PHG document.

Comment 5: "We object to the fact that this entire chapter makes no distinction between the fate of trivalent and pentavalent antimony in the human body. … Given that the clearly predominant form of antimony in drinking water can safely be expected to be the pentavalent one, we recommend reflecting the above discussed differences with respect to the choice of the relevant point-of-departure for the toxicity reference value."

Response 5: Interconversion of the two ionic forms of antimony has been demonstrated both in vitro and in vivo. When Sb(III) is administered, some studies have indicated the major metabolic pathway of antimony in humans and rats is the oxidation of Sb(III) to Sb(V) (Ogra, 2009; Kobayashi and Ogra, 2009). On the other hand, other studies have indicated that when pentavalent antimonials are administered, Sb(V) is reduced to Sb(III) in vitro and in vivo (Frezard et al., 2009; Ferreira et al., 2003; Frezard et al., 2001; Petit de Pena et al., 1990). Most notably, Petit de Pena et al. (1990)

observed that leishmaniasis patients (n = 10) injected with Sb(V) as Glucantim® (daily dose written as 17 mg ℓ g^{-1}) for 5 days had significant levels of Sb(III) in blood and urine (330.2 ± 36.0 and 10,250.8 ± 2,630.9 μg/L, respectively) compared to day zero, before treatment was started (1.8 ± 0.2 and 1.6 ± 0.1 μg/L, respectively). Sb(V) levels in the blood and urine of these patients at day 5 of treatment were 1,737.4 ± 720.0 and 19,625.5 ± 3,600 μg/L, respectively.

Also, consider the EU Risk Assessment Report (2008) Section 3.2.1.3, p. 206: "To conclude, since the results of toxicity studies using a trivalent antimony compound probably to a lesser or larger extent is the result of a mixture of trivalent and pentavalent antimony ions, and there are no conclusive evidence supporting a significant difference in toxicity between the two valences, it is decided not to differentiate between relevant and reliable toxicity results originating from tri- or pentavalent antimony studies."

Comment 6: i2a notes that OEHHA did not describe the absorption of antimony completely, especially in light of the information described in the EU (2008) report on diantimony trioxide.

Response 6: This section has been reviewed and modified to provide more details on absorption, though diantimony trioxide is not the focus of OEHHA's PHG.

Comment 7: i2a disagrees with the OEHHA statement that no modern studies on the dermal penetration of antimony were found. They cited one study on dermal absorption of diantimony trioxide.

Response 7: OEHHA has cited the results of this study in the revised PHG document.

Comment 8: i2a suggests OEHHA remove the word "probably" from the quoted ATSDR reference.

Response 8: The ATSDR quote is not included in the final PHG document.

Comment 9: i2a disagrees with OEHHA's use of outdated human studies for the hazard assessment, and offers more recent human data from their database.

Response 9: The Mayerhofer (1846) study is not being used by OEHHA for the derivation of the PHG.

Comment 10: "Reference is made to the Hext et al 90-day study of 1999. OEHHA concludes: 'Based upon the above information, a NOAEL of 421.2 mg/kg-day of antimony trioxide can be assigned.' … In the EU-RAR a NOAEL of 1686 mg/kg-day for males and 1879 for females is … derived from this Hext study. … Please explain the scientific reasons used for drawing different conclusions from the Hext study than the EU member states and OECD experts did."

Response 10: OEHHA considered the high dose in males to represent an effect level (LOAEL) from the data provided by the authors. The report found "[s]mall reductions in plasma alkaline phosphatase activity and increases in aspartate aminotransferase activity at the high dose, together with a small (ca. 10%) increase in liver weight…" The next lower dose was therefore considered the NOAEL.

The National Toxicology Program (NTP, 2005) also concluded that the mid-dose is the NOAEL, as did the National Academy of Sciences' National Research Council (NRC, 2000).

Comments 11 & 12: i2a recommends that OEHHA consider more recent data on antimony neurotoxicity and dermal toxicity, such as that cited in the EU (2008) report.

Responses 11 & 12: The EU (2008) Risk Assessment Report evaluates the data on diantimony trioxide. OEHHA found no data in the EU (2008) report on neurotoxic effects of antimony in animal studies. The report describes in detail several worker exposure studies, some of which note potential neurotoxic effects such as nerve tenderness and tingling, headaches, weakness, and prostration. Since the medium and route of exposure in these worker exposure studies are not applicable to drinking water and PHG development, OEHHA is omitting discussion of these studies in the PHG document.

Antimony's limited solubility and poor dermal penetration result in little potential for dermal toxicity. EU (2008) cites four animal studies. In two, no effects were observed; the others had methodological problems or inadequate documentation from which no conclusions could be drawn. Several reports of dermatitis after human exposures to diantimony trioxide are noted. OEHHA has cited some as representative of the literature.

Comment 13: i2a disputes OEHHA's point that, "One of the critical issues for understanding antimony toxicity remains the importance of speciation, which has not been well studied." They present summaries of a number of publications that address antimony speciation, and state, "it seems that Sb(III) is instable in tap water and rapidly oxidizes to Sb(V)." i2a further "proposes to revise this section with the references/information presented in this comment."

Response 13: The work of Filella et al. (2002a, b) and others does shed some light on the speciation of antimony in water under certain physical and chemical conditions. OEHHA has cited some of these works in its revised document.

However, OEHHA's comment relates to the effects of antimony ionic species on biological systems and the document has been revised to reflect this. Several questions remain as to the in vivo effects of trivalent vs. pentavalent forms. As the EU Risk Assessment Report (2008) points out, "There are, at least to our knowledge, at present no available toxicity studies which also include redox speciation measurements. Since trivalent antimony will oxidize to pentavalent antimony (in an oxic environment), any conclusions on differences in toxicity between tri and pentavalent antimony, based on studies without information on measured redox speciation, will therefore become speculative." OEHHA agrees.

Comment 14a: "In our opinion, it is an absolute novelty that self-experiments from one single individual, recorded in the late 19th century should supersede toxicological information derived from qualified and guideline-conform toxicity studies of the 20th and even 21st century. In particular, extrapolation from a single person to a whole population is somewhat debatable from a statistical perspective, and without an assessment of the health status of this volunteer, the relevance of his own subjective observations is not beyond question."

Response 14a: OEHHA has revised the draft PHG document and the Mayerhofer (1846) study is not being used by OEHHA as the basis for developing the drinking water PHG for antimony.

Comment 14b: "Antimony is a natural element with an ambient background concentration of 0.72 µg Sb/l (0.72 ppb) in freshwater. The proposed PHG of 0.7 ppb therefore does not make sense since the ambient background water concentration of antimony already exceeds the proposed PHG. Of note, the EU has established a Predicted No Effect Concentration (PNEC) for antimony of 113 µg Sb/l surface water (= 113 ppb). The PNEC is determined from experimentally determined endpoints divided by an appropriate assessment factor."

Response 14b: The ambient background concentration of antimony in freshwater varies from site to site and can be as low as 0.002 ppb (Shotyk, 2006). The PHG is based on potential health effects of a chemical and not on the background concentration of that chemical.

Comment 15: "It is not appropriate to use [*an additional uncertainty factor of ten for sensitive populations*] as the dose levels of APT used to induce emesis in children were similar to adults, thus indicating a lack of enhanced sensitivity. In addition, in contrast to organic molecules, antimony as a metal cation cannot undergo any structural biotransformation, thus not necessitating differences in metabolic competence to be considered."

Response 15: The first part of the comment is no longer relevant since the Mayerhofer (1846) study is not being used and emesis is not the critical endpoint. As for the issue of metabolic competence, both toxicokinetic and toxicodynamic differences exist among humans for non-metabolized substances. In the case of antimony, variations in absorption, interconversion of Sb(III) and Sb(V), excretion, and metabolism (methylation) could exist. Risk assessment guidelines do not suggest a smaller variability or uncertainty factor for metal cations.

Comments from the PET Stakeholders Ad Hoc Issues Coalition

Comment 1: "The PHG for antimony should not be based on the toxicity of antimony potassium tartrate (APT), an organometallic drug that is not found in drinking water."

"More importantly, the toxicity of APT is much greater than the toxicity of inorganic antimony, the form of antimony found in drinking water. Establishing a PHG for antimony based on the toxicity of an obsolete, organic form of APT would be like setting a PHG for lead in drinking water based on the toxicity of tetraethyl lead. Establishing a PHG for antimony on the basis of a more toxic, organic form of antimony that is never found in drinking water violates the requirement that a PHG must be established 'using the most current principles, practices and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, risk assessment and toxicology.'"

Response 1: For development of the antimony PHG, OEHHA evaluated the relevant data that were available. Most importantly, there are no acceptable human or animal studies on the pentavalent $Sb(OH)_6^-$ or the trivalent $Sb(OH)_3$ antimony species primarily found in drinking water. OEHHA's approach to critical study selection for antimony has been consistent with that of US EPA and the WHO. The earlier risk assessments by OEHHA (1997) and US EPA (1991) were both based on a 1970 rat study using potassium antimony tartrate in water (Schroeder et al., 1970). NTP (1992) also utilized potassium antimony tartrate for its studies on soluble antimony salts. Furthermore, the World Health Organization (WHO, 2003) based its drinking water guideline value for antimony on the Poon et al. (1998) study, which also used potassium antimony tartrate in drinking water, and noted that it is "critical that the study selected for guideline derivation be a drinking-water study."

Comment 1a: "[C]ritically important structural differences between a stable, bridged organometallic complex (such as APT [antimony potassium tartrate]) and a simple, readily dissociated ionic salt (like potassium bitartrate) lead to important differences in APT's chemical stability, water solubility, bioavailability (absorption and distribution) in the body and also mammalian toxicities."

Response 1a: As mentioned above in Response 1, there are no drinking water studies on antimony forms other than APT, and risk assessments by the WHO and US EPA are also based on studies using APT. Furthermore, the WHO noted that in aqueous solutions of tartar emetic (antimony potassium tartrate), inorganic anions of antimony are present along with the undissociated compound according to the law of mass action. Moreover, the acute toxicity of tartar emetic appears to be due to the fraction of ionized antimony, which is in equilibrium with antimony tartrate under prevailing conditions in the tissues (WHO, 1966).

Comment 1b: It is not appropriate to establish a PHG for antimony based on APT, an obsolete drug that is not found in drinking water. The PHG should be based on the toxicity of inorganic antimony, the form(s) of antimony found in drinking water. If a PHG is based on the toxicity of APT, then it should be the PHG for APT specifically, not antimony."

Response 1b: See Responses 1 and 1a.

Comment 1c: "The toxicity of APT is significantly greater than the toxicity of inorganic antimony, the form of antimony found in drinking water."

"The Draft PHG Document should include a review of the information in the EU risk assessment regarding important pharmacokinetic studies of the inorganic antimony substance, ATO [antimony trioxide], that were recently completed. The EU risk assessment also contains a wealth of valuable information not included in this review regarding the toxicity and pharmacokinetics of inorganic forms of antimony found in drinking water. … In addition to the difference in oxidation state and water solubility, the toxicity of APT may also be a reflection of the presence of two organic molecules of tartaric acid bridged within the APT organometallic complex. Tartaric acid itself has also been shown to produce acute and subacute toxicities."

Response 1c: The toxicity database is quite limited, and the relative absorption of the forms of antimony found in water is not well known. The EU risk assessment was focused on antimony trioxide. The toxicity of the antimony oxides is limited by their insolubility and lack of absorption after oral administration. Antimony trioxide is also not a dominant species in water due to its insolubility. However, OEHHA has added more information from EU risk assessment addressing these points. Certainly sodium tartrate

or tartaric acid can be toxic, but this occurs at about a thousand-fold higher dose than that of APT. Both sodium tartrate and tartaric acid are food additives classified as Generally Recognized as Safe by the U.S. Food and Drug Administration. In the related form of cream of tartar (potassium bitartrate), it can be found in most kitchens, used in baking.

Comment 2: "The Mayerhofer (1846) publication does not provide an adequate basis for establishing a PHG for antimony."

Response 2: The Mayerhofer (1846) study is not used by OEHHA as the basis for the final PHG.

Comment 3: "California law and prior OEHHA practice establish that the Mayerhofer publication should not be considered for quantitative risk assessment in a Public Health Goal."

Response 3: The Mayerhofer (1846) study is not used by OEHHA as the basis for the final PHG.

Comments from Sue Ellen Wright, Professor of German (translation), Kent State University

All the comments from Dr. Wright are related to the use of the Mayerhofer (1846) study for PHG development, and since this study is not used as the basis for the PHG, no specific comments and responses will be presented here.

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RESPONSES TO MAJOR COMMENTS RECEIVED FROM UNIVERSITY OF CALIFORNIA PEER REVIEWERS (FEBRUARY 2016)

Comments from Jay Goodman (Michigan State University)

Jay Goodman, Ph.D.
Professor, Department of Pharmacology and Toxicology
Michigan State University

Comment 1: "In light of the limitations (described accurately in the draft PHG) of the Schroeder *et al*. 1970 paper (e.g., a single dose of antimony potassium tartrate (APT) was used, a number of rats died due to infection and the toxicity evaluation was rather limited) it was reasonable for CAL/EPA to consider searching for another study(ies) to provide a basis for an antimony PHG. However, as described below, the Poon 1998 study is not appropriate."

Response 1: OEHHA appreciates the support for replacing the Schroeder et al. (1970) study as the critical study for PHG derivation. However, given the lack of subchronic or chronic oral animal studies using soluble antimony, OEHHA acknowledges that the Poon et al. (1998) study is not ideal but considers it the most appropriate among the studies available. The 90-day drinking water study reported by Poon et al. used soluble antimony via the oral route of exposure, had a good range of doses, and observations were well reported. Thus, it was chosen as the critical study for this PHG derivation.

Comment 2: "*OEHHA is selecting liver nuclear anisokaryosis observed in the Poon et al. (1998) study (a 90-day study involving administration of APT to Sprague-Dawley male and female rats in drinking water) as the critical endpoint.*

"Anisokaryosis can be an adaptive, not an adverse, effect."

"An adaptive change is not considered to be adverse, i.e., it is not a toxic effect. Therefore, it is not appropriate to use the anisokaryosis data from Poon 1998 as the basis for developing the antimony PHG."

Response 2: OEHHA is aware that the authors of the Poon et al. (1998) study described the histological changes observed in the liver as mild and adaptive. However, the authors also noted, "In the liver, anisokaryosis was a significant, dose-related change that approached a moderate degree of severity in all males and females of the highest dose group (Table 4). This change was still detectable at [4 weeks] recovery but with a decreased degree of severity." Poon et al. established a NOAEL of 0.5 ppm based on the histological and biochemical changes observed at 5.0 ppm. Furthermore, Poon and colleagues (Valli et al., 2000) noted, "While we recognize that these changes are adaptive, their significance needs to be considered in the knowledge of changes in serum biochemistry which include significant decreases in alkaline

phosphatase, serum creatinine, and glucose as well as decreased serum cholesterol and total protein in high-dose females. … Taken together, it would be rational to conclude that the altered serum chemistry constituted a functional reflection of altered hepatic histology."

According to Hardisty and Brix (2005), "Often the distinction between adaptive or pharmacologic responses and adverse changes is the difference in the magnitude of a change rather than a completely different mechanism or pathway. … Since the toxicologic response in animals is usually observed in a dose-dependent manner, morphologic changes that may not be considered adverse at low doses may result in serious hepatotoxicity at higher doses."

Many researchers and regulatory institutions have associated liver anisokaryosis with chemical exposure. Although anisokaryosis can be found in the livers of aging rodents, it can also be induced in response to toxic insult and has been documented as a treatment-related lesion induced by xenobiotics (NTP, 1989; Chu et al, 1990; Besteman et al, 2007; Takasawa et al, 2013; Hirata-Koizumi et al., 2008; Moir et al, 1997). Liver anisokaryosis was listed as one of the "compound-related lesions" observed in male mice exposed to hydroquinone (NTP, 1989). Furthermore, in developing the intermediate-duration Minimal Risk Level (MRL) for toxaphene, the Agency for Toxic Substances and Disease Registry (ATSDR) identified a lowest-observed-*adverse*-effect level for liver anisokaryosis as a histopathologic lesion (ATSDR, 2010).

In the NTP (1992) study, the liver was identified as the most sensitive target organ for antimony toxicity, based on histopathology and clinical pathology. This is also supported by human clinical data. The NTP (1992) report also suggested that the toxicity of APT may be linked to its accumulation in the liver. These two factors support OEHHA's determination that the treatment-related liver anisokaryosis is a biologically significant effect because it is a sign that antimony has reached the target organ and elicited a response.

Given the above information and the paucity of robust animal data on antimony toxicity, OEHHA determines that liver anisokaryosis is an appropriate critical endpoint for PHG derivation. Because anisokaryosis is a mild effect, OEHHA used a benchmark response of 10% above background in the BMD modeling, instead of the default of 5%.

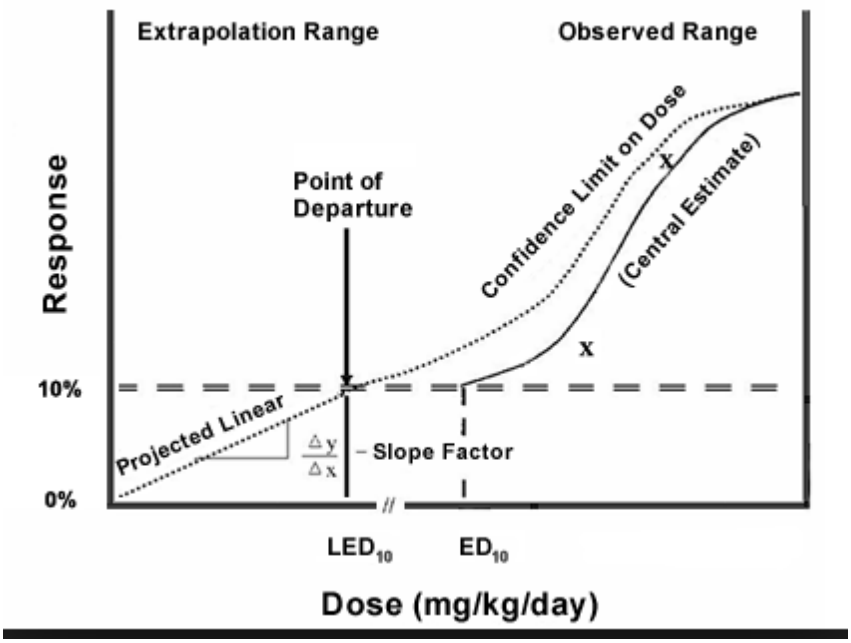
Comment 3a: "The Poon et al 1998 reference does not provide adequate justification to use the data provided in a quantitative fashion. A lack of key information makes it inappropriate to employ these data for BMD. … More statistical analysis than simply presenting averages needs to be performed in order to evaluate the extent to which the scores assigned to different treatment groups are indeed different. Additionally, and importantly, key aspects of the analysis are not presented. Specifically, there are a number of unanswered questions: 1) did a Veterinary pathologist(s) evaluate the histopathology (while not stated, this might be the case since one of the co-authors –

V.E. Valli – is from a college of Veterinary medicine); 2) how many fields were evaluated, at what magnification, which liver lobes were evaluated; 3) were the slides read blind; 4) was the histopathology evaluated by more than one pathologist and, if so, were they in agreement; 5) was the liver evaluated in a consistent fashion, e.g., by moving from the central to portal vein – this is particularly important in light of the observation by Chu 1980, p. 425, that '… increased nuclear anisokaryosis and hyperchromicity and increased binucleation were also observed. These changes appeared to be diffuse and typical of an ingested toxicant entering the liver at the portal vein and **causing most of the changes in the perivenous area** [emphasis added]?'"

Response 3a: The Poon et al. (1998) study is a peer-reviewed publication. Such methodological details are typically not included due to space limitations for journal articles. OEHHA does not have the information to answer the detailed questions raised in this comment. However, OEHHA has no reason to believe that the co-author V.E. Valli, a specialist in veterinary pathology, former Dean of the College of Veterinary Medicine at the University of Illinois, and author of the book, "Veterinary Comparative Hematopathology," would not follow the standard practices of histopathological evaluations. Assuming the slides were prepared and scored in a consistent manner, the statistically significant difference in liver anisokaryosis between the two highest doses and the control group as well as a monotonic dose-response relationship both indicate the observed changes were treatment related.

OEHHA contacted the authors of the article and acquired some histopathological grading results, which are included in Appendix I of the PHG document. As indicated by Valli et al. (2000), the validity of the grading system has been verified in prior histopathological studies (Gilroy et al, 1998). According to Valli et al. (2000), the results of the morphometric measurements by Gilroy et al. (1998) are consistent with their histological grading on the same liver tissues (Chu et al., 1995). Valli et al. (2000) also stated that "anisokaryosis and hyperchromicity of nuclei in hepatocytes in treated animals were carefully compared to the level of these changes in livers from appropriate controls."

Comment 3b: "Additionally, when a BMD approach is used a chart should be provided that indicates clearly where the actual data points are v. where extrapolations are made. It is important to be transparent. An example to illustrate this point is provided below (standard error bars should have accompanied the actual data points, denoted by 'x.')"



Response 3b: OEHHA does include all the input and output data related to BMD modeling, including the plot of the modeled dose-response curve, the BMD, and the BMDL in the document and its appendices in order to be transparent. Since the derivation of this PHG does not involve the determination of a slope factor, there is no need for a linear extrapolation.

Comment 4: "When referring to the NTP 1992 study the PHG states correctly that '…that i.p. injection is not a natural route of exposure….' It is appropriate to view the NTP data as being not suitable for deriving an antimony PHG."

Response 4: OEHHA acknowledges the comment.

Comment 5: "APT is an appropriate form of antimony to use in studies aimed at evaluating the potential toxicity of antimony."

Response 5: OEHHA acknowledges the comment.

Comments from John Pierce Wise (University of Louisville)

John Pierce Wise, Sr. Ph.D.
Professor of Pharmacology and Toxicology, University Scholar
University of Louisville

Comment 1: “Thus, the decision to replace Schroeder et al. (1970) with Poon et al. (1998) in a revised PHG for antimony is indeed based upon sound scientific knowledge, methods, and practices.”

Response 1: OEHHA acknowledges the comment.

Comment 2: “Within the Poon study LNA [liver nuclear anisokaryosis] is a mildly negative outcome, but it has wide use to indicate a pathologic change for liver toxicology. Given the stated goal of the PHG program to estimate a chemical level that poses ‘no significant health risk to individuals consuming the water on a daily basis over a lifetime,’ the choice of a mildly negative endpoint in a key target organ is scientifically appropriate. Thus, the decision to select LNA as the critical endpoint in Poon et al. is based upon sound scientific knowledge, methods, and practices.”

Response 2: OEHHA acknowledges the comment.

Comment 3: “Thus, the conversion of the histopathological data on LNA into dichotomous data for BMD modeling is based upon sound scientific knowledge, methods, and practices.”

“Thus, BDM modelling also is based upon sound scientific knowledge, methods, and practices.”

Response 3: OEHHA acknowledges the comment.

Comment 4: “Thus, concluding that the data in the NTP study support the finding of the liver as a target organ for antimony toxicity is also based upon sound scientific knowledge, methods, and practices.”

Response 4: OEHHA acknowledges the comment.

Comment 5: “Thus, basing the PHG on drinking water study utilizing APT is based upon sound scientific knowledge, methods, and practices. Furthermore, it is noted that the PHG has already been based for many years on the Schroeder et al study which used APT.”

Response 5: OEHHA acknowledges the comment.

Comment 6: “One small adjustment, in places the Poon et al study is referred to as a “90 day study” and in others as a “13 week” study. Poon et al, actually uses the terms interchangeably in their paper. However, I think the PHG should be consistent and choose one or the other. To most people 13 weeks sounds longer than 90 days and if they did a simple calculation of 13 weeks X 7 days/week, they would find a value of 91 days and then wonder if it was 90 or 91. I think for consistency with other studies presented and clarity for the reader, the PHG should only use ‘90 days’ for the Poon study and replace mention of 13 weeks.”

Response 6: The wording had been changed accordingly.

Comments from Stephen Nesnow (Stephen Nesnow Consulting)

Stephen Nesnow, Ph.D.
Director, Stephen Nesnow Consulting
Chapel Hill, NC 27516

Comment 1: “Based on the availability of drinking water dose response studies, study longevity, study design and study results, this reviewer agrees with OEHHA in the selection of the Poon et al. (1998) study as the Critical Study for further risk assessment activities and finds it based upon sound scientific knowledge, methods, and practices.”

Response 1: OEHHA acknowledges the comment.

Comment 2: “In summary, hepatic anisokaryosis is an incidental finding, does not fit the criteria of being relevant, and thus has not been proven to be the Critical Endpoint.”

“In conclusion this reviewer does not find any support in the PHG document that associates hepatic anisokaryosis with hepatotoxicity and/or necrosis and thus does not agree that it is the Critical Endpoint.”

“In this reviewer’s opinion OEHHA needs to reevaluate the use of the hepatic anisokaryosis data for BMD modeling as there is no compelling evidence linking hepatic anisokaryosis to hepatic injury. This reviewer suggests that OEHHA find an alternative

method to calculate an updated Water Guidance Value for antimony using the Poon et al. (1998) data set. Possibly, the Health Canada approach should be considered."

Response 2: Please see Response 2 to Comments from Dr. Jay Goodman of Michigan State University regarding anisokaryosis as the critical endpoint. Health Canada used the same approach as OEHHA and based its maximum acceptable concentration on histological changes in the liver observed in the Poon et al. (1998) study, though Health Canada used a NOAEL of 0.06 mg/kg-day, instead of the $BMDL_{10}$ of 0.14 mg/kg-day used by OEHHA as the point of departure (POD). Like US EPA, OEHHA prefers to use the BMD approach as the standard method in dose calculations, provided the data are amenable to BMD modeling. BMD modeling uses a statistical approach and accounts for variation in the study results, incorporating sample size into the dose-response model, and uses information from all of the doses rather than just picking one dose, the NOAEL, as the point of departure. With the BMD approach, there is more confidence in the response rate at the POD than with the NOAEL approach. In its review of US EPA risk assessment practices, the National Academy of Sciences (NAS, 2009) has similarly recognized this as a refinement that makes better use of the dose-response data available than do calculations based on NOAELs or LOAELs.

Comment 3: "OEHHA is using graded histopathological data on liver nuclear anisokaryosis for dichotomous benchmark dose (BMD) modeling to derive a point of departure (POD)."

"The approach selected by OEHHA is somewhat arbitrary, but it is a reasonable and acceptable approach."

Response 3: OEHHA acknowledges the comment.

Comment 4: "After evaluating a series of antimony studies in rodents performed by NTP (1992), OEHHA finds that while these studies are not suitable for PHG derivation, they nonetheless support the liver as the target organ for antimony toxicity."

"Based on these facts and data this reviewer agrees with the statements: '..**that it is difficult to extrapolate an intraperitoneal dose to an oral dose**" and "**OEHHA finds that .. these studies are not suitable for PHG derivation'** and this reviewer finds them based upon sound scientific knowledge, methods, and practices."

"In aggregate, the experimental evidence supports the PHG statement '**These studies…support the liver as the target organ for antimony toxicity.'** This reviewer agrees with this statement as it is based on the NTP (1992) studies as well as relevant additional information from feeding studies using antimonials and finds the statement based upon sound scientific knowledge, methods, and practices."

Response 4: OEHHA acknowledges the comment.

Comment 5a: "While the PHG document's conclusions regarding the relative toxicity of valence states of antimony may be valid, this reviewer finds that the bases of these conclusions are grounded on limited data related to very specific toxicities, shock and pneumonia. The PHG document's statement should be revised to reflect this, or a new analysis undertaken to review and analyze the complete literature on this subject. These comments also pertain to the validity of the statement in the OEHHA Request for Review: 'Generally trivalent antimony (Sb(III)) is more toxic than pentavalent antimony (Sb(V)). APT, which is highly water soluble and contains Sb(III), likely has the greatest oral toxicity among the many compounds of antimony.'"

"The PHG document restates a conclusion in the 2008 EU diantimony risk assessment report: 'To conclude, since the results of toxicity studies using a trivalent antimony compound probably to a lesser or larger extent is the result of a mixture of trivalent and pentavalent antimony ions, and there are no conclusive evidence supporting a significant difference in toxicity between the two valences, it is decided not to differentiate between relevant and reliable toxicity results originating from tri- or pentavalent antimony studies.' Isn't this statement and the statement regarding the relative toxicities of antimony compounds with different valence states somewhat in conflict?"

Response 5a: OEHHA agrees that the text is confusing. The statements have been revised as follows: According to the World Health Organization, Sb(III) may be more toxic than Sb(V) and the inorganic compounds are generally more toxic than the organic compounds (WHO, 2003). APT, which is highly water soluble and contains the trivalent form of antimony (Sb(III)), may have greater oral toxicity than some other compounds of antimony. Because both the Poon et al. (1998) study and the WHO (2003) guidelines are based on APT, they acknowledged that their results would probably overestimate the risk from the predominant antimony species in drinking water, the pentavalent form of antimony (Sb(V)). However, as indicated in the EU (2008) report, "[T]here [is] no conclusive evidence supporting a significant difference in toxicity between the two valences." Thus, it is reasoned that the determination of a drinking water level based on the Poon et al. (1998) study would likely be health protective.

Comment 5b: "Based on the information presented in the PHG document and the recently published research, this reviewer concludes that the choice of APT, the trivalent form of antimony as used in the Poon et al. (1998) study is appropriate for use in this risk assessment and is based upon sound scientific knowledge, methods, and practices."

Response 5b: OEHHA acknowledges the comment.

Comment 6: “There are five recent publications that this reviewer cites in Statement 5 that should be considered in the PHG document: Sun et al. (2000), Hansen et al. (2011), Lòpez et al. (2015), Hashemzaei et al. (2015) and Bento et al. (2013). In addition, the PHG document should cite for completeness a recent study on antimony (as meglumine antimoniate) in rats that found that meglumine antimoniate was transferred via the placenta and impaired prenatal growth and fetal and/or neonatal viability at the highest dose. (Coelho DR, De-Carvalho RR, Rocha RC, Saint’Pierre TD, Paumgartten FJ. Effects of in utero and lactational exposure to Sb V on rat neurobehavioral development and fertility. Reproductive Toxicology. 2014 Dec 31;50:98-107.)”

Response 6: Citations of these studies were added to the PHG document.

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RESPONSES TO MAJOR COMMENTS RECEIVED, SECOND COMMENT PERIOD (AUGUST 2016)

Comments from Michael Huber, P.E., DoD Regional Environmental Coordination (DoDREC 9) Program Manager, San Diego, CA

Comment 1: "[W]e request additional technical information and justification for the use of an uncertainty factor (UF) of 30. Application of the UF above the default of 10 for variation in the human population is not typical. It seems inconsistent with practices and methods described in OEHHA Guidelines, specifically the Technical Support Document for the Derivation of Noncancer Reference Exposure Levels dated 2008. These Guidelines describe some instances where this UF may be higher than the default, but we are unsure of the specific rationale as compared to what is recommended in the Guidelines. Given the discussion of pharmacokinetics in children provided in the Draft Public Health Goal document, where it is stated that 'antimony exposure is significantly lower in children than in adults given the same weight-adjusted dose'; it does not seem necessary to raise the value of the UF to be protective of these receptors. Reducing the UF to 10 would be in keeping with standard practice and would result in an increase to the proposed PHG at least by a factor of three to 3.0 micrograms per liter (ppb)."

Response 1: The statement cited about antimony exposure in children is the conclusion of the authors of a single study comparing children and adults treated with meglumine antimoniate by intramuscular injection (Cruz et al., 2007). The study authors concluded that the lower exposure observed in children was primarily due to a higher antimony clearance rate as determined by plasma concentrations of antimony. However, the antimony PHG for drinking water is based primarily on oral exposure and variations in gastrointestinal absorption, interconversion of SbIII and SbV, excretion, and metabolism (methylation) could exist. A factor of 10 is applied for the toxicokinetics component of the intraspecies uncertainty factor because of the lack of human kinetic data to allow for diversity, including infants and children, as described in OEHHA's guidelines (OEHHA, 2008). An uncertainty factor of 30 is therefore used for variation in the human population, which is consistent with OEHHA's guidelines (OEHHA, 2008).

Comment 2: "We are also concerned with the use of accumulation of antimony in organs as an apparent weight of evidence, since there are no described associated toxic effects in the technical support document."

Response 2: The accumulation of antimony in organs is not considered by OEHHA as an apparent weight of evidence for liver toxicity. The PHG document provides a comprehensive review of studies demonstrating adverse liver effects in both humans and animals following antimony exposure. Furthermore, the NTP identified the liver as the most sensitive target organ for antimony toxicity, based on histopathology and

clinical pathology (NTP, 1992). The accumulation of antimony in the liver demonstrates that it is absorbed via oral ingestion and can accumulate appreciably in the target organ.

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