Responses to Major Comments on Technical Support Document

Public Health Goal
For
Chlorite
In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Branch
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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 the disinfection byproduct chlorite in drinking water, based on the two review drafts. Changes have already been made in response to these comments, and have been incorporated into the final version 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 MAJOR COMMENTS RECEIVED

[Comments on the first posted draft]

Comments from Sodium Chlorite/Chlorine Dioxide Panel of the American Chemistry Council (August, 2007)

Note: Member companies of the Panel are: Ashland Inc., BASF Corporation, Bio-Cide International Inc., Eco Lab Inc., ERCO Worldwide Inc, International Dioxcide Inc (DuPont), Occidental Chemical Corporation, Sabre Oxidation Technologies, Inc., and SIEMENS Water Technologies Corporation.

Comment 1: *Use of the Mobley study as the primary basis for setting the PHG is inappropriate for a number of reasons, including*: "The Mobley study does not represent the current principles, methods and practices for this type of study. … The Panel toxicologists concluded that the data are interesting, but hard to interpret due to a lack of experimental details and methodological problems."

Response 1: Risk assessment utilizes all relevant data; there is no restriction to studies carried out according to study guidelines for regulatory submissions. This appears to be a well-conducted study, and the behavioral data are relatively clear. We agree that the significance of a delay in development of exploratory activity in newborn rats can have many causes and is subject to various interpretations, which is discussed in the PHG document.

Comment 2: "If the authors tested the same rats every day as depicted in Figure 1 (post conception days 36, 37, 38, 39, and 40 which is equivalent to lactation days 15-19), then the testing environment is no longer novel, which is necessary in order to evoke an appropriate exploratory behavior. In addition, the number of counts on post conception days 36 and 37 (equivalent to lactation days 15-16) are very low (less than 1 movement in 10 minutes); and may reflect an insensitivity of the sensor to detect their movement or an inappropriate method for their developmental age."

Response 2: The rats in the study of Mobley *et al.* (1990) are housed in a dual-chamber apparatus with an opening between the chambers small enough that only the pups can go through it. As the pups mature, they begin to move around and spend more time at further distances from their dam. Novelty and habituation are not relevant factors in this developmental pattern. Beam-crossings in the secondary chamber are measured continuously and reported per 10-minute interval, giving per-litter activity measurements. This continuous activity measuring system has been successfully used in the demonstration of developmental delays caused by other toxicants such as lead (Crofton *et al.*, 1980), and there is no particular reason to doubt the validity of the experimental paradigm.

Comment 3: "The authors report that the litter with the dam was evaluated, however the number of pups per litter was not stated, and the interaction between the individual pups

and the dam during motor activity evaluation could confound the results of the evaluation."

Response 3: Mobley *et al.* (1990) state that the litters were culled to 8 pups. Dams could not enter the secondary chamber and therefore could not affect activity counts in that chamber.

Comment 4: "In addition, there was no evaluation of learning and memory, or of individual pup behavior in an open field arena as required by current methods and practices."

Response 4: Agreed. We are not aware of any studies of the effect of chlorite on the development of open-field behavior, and have cited the CMA (1996) study, which has been interpreted by U.S. EPA and ATSDR as showing a significant effect on learning in rat pups after exposure of their dams to sodium chlorite during gestation.

Comment 5: "The authors [Mobley *et al.*] report the day of eye opening, however, under current methods and practices, determination of additional measures of maturation such as vaginal opening and preputial separation are also required."

Response 5: We note effects of chlorite on these developmental parameters also, as reported by Gill *et al.* (2000), based on the CMA (1996) study.

Comment 6: "Under current practices, evaluation of hormonal concentrations needs to occur on a specific, exact postnatal day instead of a range of postnatal days, with a larger number of offspring and litters evaluated. Typically, if blood has to be pooled, it is pooled per litter on at least 2 pups/sex/litter, and at least 10 litters evaluated. The historical control range needs to be included. The normal ranges for pups of this age should be provided."

Response 6: Comments noted. The results of the hormonal assays in the study of Mobley *et al*. (1990) were not utilized in determining a critical effect level for chlorite.

Comment 7: "The current guideline, OPPTS 870.6200 (Neurotoxicity Screening Battery), includes guidance on the conduct of a motor activity study. This guidance requires that positive control data be provided to demonstrate the sensitivity and reliability of the activity measuring device and testing procedure. These data should demonstrate the ability to detect increases or decreases in activity. Mobley et al do not provide positive control data. Also, the Mobley et al data shows only day-to-day increases in motor activity."

Response 7: OPPTS 870.6200 was finalized in 1998, and no studies have been made available on chlorite effects since the guideline was developed. The Mobley *et al.* (1990) data show the expected pattern of increasing activity with age; the apparatus is as sensitive to decreases as to increases in activity. However, again, risk assessment is not limited to studies carried out according to guidelines for regulatory submissions.

Comment 8: "In Mobley, et al., the protocol and equipment used for exploratory activity measurement is credited to Crofton, K. M., et al. "Developmental Delays in Exploration and Locomotor Activity in Male Rats Exposed to Low-Level Lead," *Life Sci.* 26:823-31 (1980). This reference appears to include information on multiple behavioral test methods, yet Mobley, et al. used only one method. Further, Crofton, et al. is not referenced as a resource in any current guideline for behavioral testing. Clearly, the use of exploratory activity in the Mobley study is not representative of current principles, methods and practices for evaluation of motor activity."

Response 8: The subsequent development and standardization of neurotoxicity test procedures does not invalidate the results of tests using other methods.

Comment 9: *Based on a phone conversation with Dr. Mobley on July 31, 2007,* "Dr. Mobley himself does not believe it is appropriate to use his study as the definitive basis for establishing a PHG for chlorite. He does believe the study should be used as one data point in the context of other existing information that would be required to provide a robust evaluation of the overall safety of chlorite."

Response 9: The study of Mobley *et al.* (1990) has indeed been used in this PHG as one data point in the context of other existing information in the risk assessment for chlorite.

Comment 10: "…understandably, Dr. Mobley did not recall all of the details of the statistical analysis. The publication states that the data were analyzed using an analysis of variance (ANOVA). However, it is not clear that the exploratory activity data were normally distributed, a key factor for using an ANOVA. Dr. Mobley recalled that the statistical analyses were performed by another individual (not an author of the paper), and he did not recall considering the shape of the distribution curve." "According to the publication, the sample size was only 6 per group. The statistical analysis did not take into account the full litter size as a factor (e.g., unit of measurement was the culled litter, not individual pups). Each culled litter was considered "equal", and did not include analysis of initial litter size as a potential factor in the results. Furthermore, since no individual data or measurements of variance were provided, it is not possible to evaluate the appropriateness of the statistical analysis."

Response 10. We agree that the relatively small group sizes and lack of details on the statistical methods lends additional uncertainty to the evaluation, which has been noted in the revised document.

Comment 11: "Other studies have reported that rats have an aversion to the taste of chlorite in drinking water. Dr. Mobley's study did not report measuring water consumption. However, Dr. Mobley remembered measuring water consumption, and he did not remember any of the details as to whether statistical analysis was performed to account for differences in water consumption. It is possible that the slight "effect" of chlorite on exploratory activity may have been related to taste aversion to chlorite in

water. The pups may have been more inclined to stay with the dams before they were weaned in order to gain more milk. In other words, the pups exposed to chlorite may have been more inclined to stay in the nesting area of the cage due to thirst. This is consistent with the observation that the differences in exploratory activity no longer existed after weaning in the Dr. Mobley's study."

Response 11: According to Mobley *et al.* (1990), "Food and drinking water of dams and body weights of both dams and pups were monitored throughout the experiment." No significant effects of the treatments were reported on these parameters. No decrease in total litter weight occurred in dams exposed to sodium chlorite, although there was a small decrease in the total litter weight of dams exposed to chlorine dioxide. Decreased body weights and decreased body weight increases are the usual response to aversive effects from bad-tasting drinking water. Thus the data provide no basis for the speculation above.

Comment 12: "The study was not peer reviewed, nor did it employ good laboratory practices (GLP) The Mobley study was published in a conference proceeding. The last paragraph of the report under acknowledgments states: "…EPA, Grant CR-809618, this manuscript has not been subjected to the Agencies peer and administrative review and, therefore, does not necessarily reflect the views of the Agency, and no official endorsement should be inferred."

Response 12: We agree that lack of publication in a peer-reviewed journal is one important factor to be considered in assessing the credibility of this or any study. Research studies conducted under U.S. EPA grants to universities are not customarily carried out under GLP procedures and are not subject to U.S. EPA administrative review before publication.

Comment 13: "According to Health and Safety Code 116365, a PHG should be derived from a risk assessment "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." The fact that current risk assessments by other agencies have not used the Mobley et al. study as the pivotal study is further evidence that the proposed use of this study as the critical study is not consistent with "the most current principles, practices, and methods." The Panel has reviewed a number of international and domestic risk assessments for sodium chlorite. None of these has chosen to use the Mobley study to define the pivotal endpoint. Where the Mobley study has been considered at all, it has been as a component of a Weight-of Evidence approach.

Response 13: The U.S. EPA (1994) drinking water criteria document cited the 20 ppm concentration in the Mobley *et al.* (1990) study as a LOAEL, and from this value derived their RfD of 0.003 mg/kg for chlorite, the drinking water equivalent level of 0.11 mg/L, and an MCLG of 0.08 mg/L. The U.S. EPA risk assessment was later revised (U.S. EPA, 1998a,b,c) to utilize the CMA (1996) study, with a higher NOAEL and a lower uncertainty factor. We do not agree that the CMA study fully substitutes for or can replace the study of Mobley *et al*., since different test procedures were used in the two

studies, and the simple learning paradigm of the CMA study (habituation to a an auditory tone) measures a completely different behavioral/neurological response. We have discussed both studies in the PHG document, and consider them both to be part of the weight-of-evidence for significant neurodevelopmental effects of chlorite.

Comment 14: "EPA, ATSDR and others have all used the weight of evidence approach, considering all relevant studies (including Mobley), and have reached the same NOAEL as in the proposed PHG, but did not need to apply an additional arbitrary 10X safety factor for extrapolation from a LOAEL."

Response 14: The U.S. EPA (1994) risk assessment for chlorite derived an RfD of 0.003 mg/kg-day and used an uncertainty factor of 1000 (the same approach as OEHHA). After the results of the CMA study were published (CMA, 1996 and Gill *et al.*, 2000), the subsequent U.S. EPA risk assessments put more weight on this more recent and more detailed study. One critical issue appears to be whether the CMA study truly contradicts the results of the study of Mobley *et al.* (1990). We concluded that it does not.

In the U.S. EPA (2000) toxicological review of chlorine dioxide and chlorite, U.S. EPA concludes, "The principal study [CMA, 1996] is supported by the developmental studies by Orme et al. (1985), Taylor and Pfohl (1985), Mobley et al. (1990), and Toth et al. (1990), wherein rats administered chlorite or chlorine dioxide at similar dosages in drinking water also showed alterations in exploratory and locomotor behavior and reduced brain weights (NOAELs of 3 mg/kg-day; LOAELs of 14 mg/kg-day)." Thus U.S. EPA continued to cite the study of Mobley *et al*., merely choosing to discount the relevance of the statistically significant effects at the dose of 3 mg/kg-day (U.S. EPA, 1998c, p. 14; U.S. EPA, 2000, p. 33). The ATSDR (2004) review took a similar approach. On the other hand, the risk assessment for the U.S. EPA Reregistration Eligibility Decision (RED) for disinfectant uses of chlorine dioxide prepared by the Office of Pesticide Programs Antimicrobials Division (U.S. EPA, 2006a,b) did not specifically cite the Mobley study. The latter context puts more weight on studies conducted for pesticide regulatory submission.

The other important issue of the appropriate safety factor is addressed by U.S. EPA for the chlorine dioxide and sodium chlorite toxicity review in IRIS (U.S. EPA, 2000) as:

> "The composite uncertainty factor (UF) of 100 includes a factor of 10 to account for uncertainties associated with interspecies extrapolation and a factor of 10 for intrahuman variability. Because the critical effect is developmental toxicity in a database that includes chronic studies, it is not necessary to use an additional uncertainty factor to account for use of a less-than-lifetime study. UF=100, MF=1"

This decision is consistent with the policy described in the risk assessment conducted for the chlorine dioxide RED as follows:

> "Since the time of this 1999 recommendation, policy guidance was issued in September of 2001 through the Health Effects Division, Office of Pesticide Programs regarding the determination of the appropriate FQPA safety factor in tolerance assessment. This guidance states that whereas in the past "...OPP has

routinely applied an additional FQPA safety factor where data on a pesticide shows increased susceptibility or sensitivity (either qualitative or quantitative) in the developing organism," It is now the intent that "...OPP will now put greater emphasis on analyzing the degree of concern and, rather than apply an additional safety factor based solely on the identification of heightened sensitivity or susceptibility, will conduct a case-by-case weight of evidence approach that qualitatively examines the level of concern for sensitivity / susceptibility and assess whether traditional uncertainty factors already incorporated into the risk assessment are adequate to protect the safety of infants and children. Using this approach, in many cases the concerns regarding pre- and postnatal toxicity can be addressed when a Reference Dose (RfD) or Margin of Exposure (MOE) is based on the pre- or postnatal endpoints in the offspring."

"In the case of chlorine dioxide, the endpoint selected for both dietary and non-dietary exposures was based upon adverse effects observed in offspring from developmental and reproductive toxicity data. Consistent with the approach used by the EPA's Office of Water for use of chlorine dioxide as a drinking water disinfectant (Federal Register Vol. 63, No. 61, pages 15673-15692, March 31, 1998) and the updated guidance on selection of a safety factor under FQPA, the endpoint selected for assessment of risk from dietary and non-dietary exposure to chlorine dioxide is felt to be protective of potentially susceptible populations including children, based upon the selection of an endpoint and effects observed in offspring and the use of an NOAEL value based on those effects. Therefore it can be concluded that an additional safety factor under FQPA is not necessary in this case and that the traditional uncertainty factor (MOE) of 100 for intraspecies and interspecies variation will support the safety standard of 'reasonable certainty of no harm' as required by the FQPA statute for food-use pesticides."

This adequately explains the U.S. EPA decision to decrease the total UF/MF from 1000 in the 1994 risk assessment to 100 in the later versions. However, the OEHHA risk assessment added another factor of 10 to the combined UF for extrapolation from a NOAEL to a LOAEL. This standard approach was avoided by U.S. EPA (1998c) with the statement about the study of Mobley *et al.* (1990) that, "Reviewing the results of this study relative to the finding of the newer developmental studies in the database, suggests the NOAEL for neurodevelopmental behavior effects in rats for this study is approximately 3 mg/kg-day and the LOAEL is 6 mg/kg-day." It was restated in U.S. EPA (2000) as "The changes at 3 mg/kg-day were small, whereas changes observed at 6 mg/kg-day were more consistent with findings from several other studies." We agree that the changes were small, and that these changes were observed at a slightly lower dose than in other studies. We do not agree that it is therefore appropriate to ignore significant results and declare the results to represent a NOAEL. However, we have concluded that these small changes should not require a full uncertainty factor of 10 to extrapolate from a LOAEL to a NOAEL, and propose a UF of 3 in the revised PHG document for this extrapolation.

Comment 15: "In the Proposed PHG, the reviewers indicated that they did not know why the Mobley study was not used in the ATSDR and IRIS risk assessments. Explanations

for this conclusion are found in several references, not included in the Proposed PHG. These conclusions and the references are explained in detail below."

Response 15: The different interpretations are discussed in response to Comment 14.

Comment 16: "The World Health Organization developed provisional guidelines for chlorite in drinking water in 2005. The provisional guideline value is calculated as 0.7 mg/L. In addition the WHO document states

> "This guideline value is designated as provisional because use of chlorine dioxide as a disinfectant may result in the chlorite guideline value being exceeded, and difficulties in meeting the guideline value must never be a reason for compromising adequate disinfection." (WHO 2005 p 18-19)"

Response 16: Reference to the WHO background report on chlorite and chlorate in drinking water has been added to the PHG document. The WHO provisional guideline for disinfection appears to be equivalent in principle to an MCL, and thus makes an explicit risk/benefit analysis. California Health and Safety Code 116365 directs OEHHA to set PHGs based exclusively on public health considerations, which are to be "set at the level at which no known or anticipated adverse effects on health occur, with an adequate margin of safety."

Comment 17: "WHO also stated that the NOAEL for the Mobley study is 3 mg/kg of body weight per day. … WHO assigned the Mobley study a NOAEL because the TERA Risk Assessment was considered in their analysis."

Response 17: Yes, that appears to be correct.

Comment 18: "A draft SIDS Initial Assessment Report (SIAR) was prepared by WRc under the auspices of the CEFIC Sodium Chlorite HPV group for submission in response to the to the OECD HPV Chemicals Programme. … The draft document looked at the same data set reviewed in the Proposed Public Health Goal Paper. Again, a NOAEL of 3 mg/kg body weight/day was chosen for all development studies. The draft SIAR states that four developmental studies from 1985 to 1990, including the Mobley study should not be considered key or critical. The document explains that these developmental studies should not be considered critical because they had limited protocols, were not GLP, and had limited interpretation of results. After considering comments from nine countries, OECD published the SIDS Initial Assessment Profile For SIAM 23, Sodium Chlorite 7758-19-2 and Chlorine Dioxide 10049-04-4 (October 2006). This document is included in this submission and is available at http://cs3-hq.oecd.org/scripts/hpv/. The published document lists a NOAEL for hematotoxicity effects, based on the two-generation study, of 3 mg/kg body weight/day."

Response 18. We thank the commenters for this additional reference. It is interesting that these reviewers are discounting all the behavioral results, whereas all other reviewers consider them of significance.

Comment 19: "EPA-OPP developed a risk assessment for sodium chlorite as part of the Reregistration Eligibility Document (RED) for the continued use of sodium chlorite as an antimicrobial pesticide." *A chronic NOAEL of 3 mg/kg-day and a UF of 100 was applied in this document.*

Response 19: Yes. This was summarized above in the response to comment 14.

Comment 20: *For biocidal product registration in Europe, SafePharm Laboratories, acting for the European Chemical Industry Council (CEFIC), has prepared* "extensive dossiers of toxicological data and other information" *on chlorite. SafePharm Laboratories reports that:*

> "We haven't used the Mobley 1990 report in the dossier. It was our intention to submit it in the IUCLID only, as it had been given a reliability of 3 ("not reliable", under the Klimisch rating system) in the HPV dossier.
>
> The studies we used in the dossier for chlorite are as follows:
>
> A6.8.1: Developmental toxicity - Irvine, L.F.H. (1990) Sodium chlorite rabbit teratology study (drinking water administration). Toxicol Laboratories Ltd., Report No. CMA/3/90 (NOAEL = 9 mg chlorite/kg bw/day)
>
> A6.9: Neurotoxicity - Gill, M.W., Swanson, M.S., Murphy, S.R. and Bailey, G.P. (2000) Two-generation reproduction and development neurotoxicity study with sodium chlorite in the rat. Journal of Applied Toxicology, 20: 291-303 (NOAEL = 2.9 mg chlorite/kg bw/day, according to the WHO)."

Response 20. We thank the commenters for this additional information.

Comment 21: "In the PHG calculation, estimated water consumption rates for infants were used in place of the adult consumption rates as used by the EPA. Accordingly, The PHG assumes a water (and chlorite) consumption rate, approximately 7 times the rate used by the EPA. The total infant consumption rate is composed of both direct water (tap water) and indirect water (milk, juice and formula). In fact, water consumed by infants is predominantly as a component of another food (indirect water) as opposed to water consumed as water. This conclusion is supported in detail in comments submitted to the US EPA by the Sodium Chlorate Reregistration Task Force in response to the Preliminary Risk Assessment for Sodium Chlorate, (EPA-HQ-OPP-2005-0507-0017.1). In these comments, infant formula was calculated to account for 93% of the total water consumed by infants."

Response 21: The California Safe Drinking Water Act specifically directs OEHHA to consider potentially susceptible populations, including infants and children. For this reason, and because the endpoint of concern is developmental, we considered it necessary to calculate exposures based on infant consumption rates.

Comment 22: "Components of infant formula are known to react with and remove chlorite and chlorine dioxide from the product as reported in Ozawa and Kwan, (1987), and Simpson (2002). This has been further demonstrated in laboratory experiments, as detailed in 3.2 below. This means that while the quantity of liquid per body weight consumed by infants may be greater than that for adults, the amount of chlorite consumed per body weight is actually less. Accordingly, the PHG calculations should be adjusted to reflect this fact." "A recent study by ERCO Worldwide (Tran, T. V. 2006) has established that chlorite ions, at concentrations up to 20 mg/L, are completely reduced to chloride within 30 minutes of introduction into infant formula."

Response 22: OEHHA has not been able to determine the relevance of the cited observations to actual infant exposures. We concur with U.S. EPA (2006b), which says "The Agency is not currently able to quantify the reduction of exposure to chlorite that occurs due to binding of chlorite with ingredients present in the baby formula. … The Agency will require additional data on the breakdown of chlorite in baby formula as confirmatory data" (p. 49). A description of this factor has been added to the PHG document.

Comment 23: "The proposed PHG includes a factor of 10 for intraspecies variability (sensitive populations) and then "double corrects for sensitive populations…by using 0.211 L/kg-day of water consumed by a child six months old." … "EPA addresses this issue in the response to comments for the Disinfection Byproducts Rule in 1998.

> "The MCLG and MRDLG presented for chlorite and chlorine dioxide are considered to be protective of susceptible groups, including children, given that the RfD is based on a NOAEL derived from developmental testing, which includes a two-generation reproductive study. A two-generation reproductive study evaluates the effects of chemicals on the entire developmental and reproductive life of the organism. Additionally, current methods for developing RfDs are designed to be protective for sensitive populations. In the case of chlorite and chlorine dioxide a factor of 10 was used to account for variability between the average human response and the response of more sensitive individuals. In addition, the important exposure is that of the pregnant and lactating female and the nursing pup. The 2 liter per day water consumption and the 70 kg body weight assumptions are viewed as adequately protective of all groups." (63 FR 69404)

Response 23: OEHHA considers the factor of 10 for human variability to accommodate differences in toxicodynamics and toxicokinetics among individuals, including infants and children, pregnant women and their fetuses, and the elderly. This factor of 10 does not include differences in *exposure* within the human population. The water consumption estimate used by U.S. EPA (2 L/day for a 70 kg adult) has been said to correspond to about the 70% percentile of adult drinking water consumption. OEHHA does not agree that this water consumption value is appropriately protective against developmental effects in infants; OEHHA uses a value corresponding to the upper 95th percentile community water consumption rate of the specific human population of concern.

Comment 24: "Additional protection for children is addressed in the [U.S. EPA] response to comments for the Disinfection Byproducts Rule in 1998.

> "Finally, EPA disagrees that an additional safety factor should be applied to provide additional protection for children or that drinking water consumption relative to the body weight of children should be used in developing the MCLG. The MCLG and MRDLG presented for chlorite and chlorine dioxide are considered to be protective of susceptible groups, including children, given that the RfD is based on a NOAEL derived from developmental testing, which includes a two-generation reproductive study." (63 FR 69404). … Therefore it can be concluded that an additional safety factor under FQPA is not necessary in this case and that the traditional uncertainty factor (MOE) of 100 for intraspecies and interspecies variation will support the safety standard of 'reasonable certainty of no harm' as required by the FQPA statute for food-use pesticides.""

Response 24: The U.S. EPA decision appears to be consistent with their interpretation of the toxicology data and the Food Quality Protection Act (FQPA), for determination of food tolerances for chlorine dioxide or chlorite. OEHHA does not utilize the FQPA uncertainty factor for risk assessment of chemicals in drinking water.

Comment 25: **"**On page 12 of the PHG Proposal, OEHHA indicates that the independent reviewers of the 2-gen study believed that the NOAELs and LOAELs for certain endpoints should be revised. An examination of the external peer review paper, and the subsequent regulatory actions taken by EPA following this review indicates that the NOAELs were, in fact, lowered to the values used by the EPA in establishing the MCLG for chlorite."

Response 25. One reviewer suggested that the LOAEL for blood changes was 3 mg/kg; another, that the LOAEL for blood changes and decreased sperm counts would be half the lowest dose tested; and another suggested that the 3 mg/kg dose was a NOAEL, but not a NOEL. We agree that U.S. EPA responded to these comments, but do not agree that they lowered the MCLG to the lowest value suggested by these reviewers, nor that the U.S. EPA's responses make the points that were being made by the reviewers therefore moot. We consider that the equivocal nature of the effects observed at 3 mg/kg-day is supportive of the effects observed at the same dose in the study of Mobley *et al.* (1990).

Comment 26: "The document states that the state of Maine has established a drinking water guideline for chlorite of 7 ppb. (PHG, Pg. 27). This statement is incorrect. The current Maximum Exposure Guideline for chlorite is 210 ppb."

Response 26: We were unable to confirm either value. The State of Maine "Rules Relating to Drinking Water" (effective Sept 20, 2006) merely cites the Federal Register regulations for disinfection byproducts, which would make their state MCL 1.0 mg/L. The reference to Maine has been removed from the PHG.

Comment 27: "The listing of sodium chlorite producers is incorrect (PHG, Pg. 4). Currently, Occidental Chemical is the only producer in the US. ERCO Worldwide produces sodium chlorite in Canada and is the only other North American chlorite producer."

Response 27: This correction has been incorporated into the document.

Comment 28: "Conclusions: Following our review of the proposed PHG, and in view of the new data provided, the Panel requests that OEHHA reconsider its PHG proposal. A PHG similar to and consistent with US EPA's MCLG and MCL of 0.8 and 1.0 mg/L, respectively, is scientifically justifiable. The Panel suggests that OEHHA abandon the Mobley study as the pivotal study in the determination of the PHG. The Mobley study and the end point relied on by OEHHA are not consistent with "the most current principles, practices, and methods". The Panel believes that the NOAEL of 3.0 mg/kg/day is supportable based on the weight of evidence approach as used in other risk assessments. There is no justification for imposition of a 10X safety factor to extrapolate from a LOAEL to a NOAEL. The Panel also suggests that, while infants may well consume more liquids per body weight than do adults, they do not consume as much chlorite, since the chlorite will be largely reacted out before it is consumed. Accordingly, the PHG calculations should be adjusted to reflect this fact.

Response 28: OEHHA believes that the available data do demonstrate reversible neurodevelopmental effects in rats at an oral dose as low as 3 mg/kg-day. Because this is not a severe response, and the available studies show reversibility of effect, we conclude that the uncertainty factor for extrapolation of a LOAEL to a NOAEL could be decreased from 10 to 3. Because of rounding, this increases the proposed PHG from 10 ppb to 50 ppb.

[comments on the second draft, posted June 2008]

Comments from Jonathan T. Busch for the Sodium Chlorite/Chlorine Dioxide Panel, American Chemistry Council (Sept. 2008)

Comment 1: "The Panel agrees with OEHHA's decision to rely on the CMA (1996) two-generation rat reproduction study as the critical study to establish the Public Health Goal (PHG) for chlorite. As noted in the Panel's previous comments, the Mobley *et al.* (1990) study has significant limitations that make it inappropriate to serve as the critical study for determining a PHG for chlorite."

Response 1: We agree.

Comment 2: "While the Panel agrees with the decision to use the CMA study as the critical study, it however, disagrees with OEHHA's interpretation of the results of that key study. The Panel has two major concerns regarding OEHHA's Draft Report, and its interpretation of the results. Those two concerns are: (1) the lowest dose in the CMA

(1996) study is a NOAEL (not a LOAEL), and (2) the exposure assessment by OEHHA for infants should take into account the high reactivity and degradation of chlorite in infant formula. Careful consideration of these two factors raises the proposed PHG from 50 ppb to approximately 1,000 ppb, which is more scientifically justifiable."

Response 2: A detailed response to these issues is presented below.

Comment 3: "…the study authors concluded that the lowest dose is a NOAEL because the differences in hematological values from the control values "were very small, were within normal ranges, and were considered not to be of toxicological significance. The Draft Report takes issue with the study authors' conclusion that the hematological values are within normal ranges because (1) "the CMA (1996) study provided historical [control] data only for the pooled range of 0 to 3 months of age" and (2) "the hematological parameters for all control and treated day 25 postnatal pup groups were outside of these historical ranges for red blood cell counts (RBC), hemoglobin (Hb), packed cell volume (PCV), and mean corpuscular hemoglobin concentration (MCHC)." It is unfortunate that historical control data were not available for specific age groups to judge whether the postnatal day 25 pup values were outside the appropriate historical control range. Indeed, the fact that the RBC, Hb, PCV and MCHC values for all control and treated postnatal day 25 pups were outside the historical range simply suggests that the historical controls are not reflective of postnatal day 25 pups."

Response 3: OEHHA does not think it is appropriate to accept the authors' interpretation without the supporting data. In our opinion, the constellation of effects on hematological parameters in the CMA (1996 rat study are not an incidental observation (a random statistical fluctuation), and therefore must be assumed to represent a hematological endpoint. Similar hematological effects have been observed in other studies, such as those of Bercz *et al.* (1982) in monkeys and Harrington *et al.* (1995) in rats.

Comment 4: "Significantly, the Draft Report does not adequately address the study authors' conclusions that the differences at the lowest dose were "very small" and "considered not to be of toxicological significance." It is also important to note that these differences resolved by day 90. Recent communications with one of the study authors[5] reaffirmed their conclusion that although the differences may be statistically significant, they should not be considered to be clinically or toxicologically significant. Blood measurements such as these naturally have a wide variation based on a variety of parameters. The authors' position is that it is a misinterpretation of these data to find that these small statistical changes are clinically significant."

Response 4: We do not agree that significant effects of a reactive chemical on red blood cells should be considered to have no toxicological significance. Furthermore, smaller, but still significant decreases in PCV were also observed at all doses at 90 days, as shown in Table 5. We believe that these hematological changes in the developing animals are a concern in the context of the spectrum of effects in neonates, and serve to establish the low end of the dose-response range for chlorite.

Comment 5: "Additionally, it is important to recognize that the Williams test (i.e., the statistical test employed to evaluate the hematological data) is a trend-sensitive test. Hence, the Williams test is not necessarily appropriate for a NOAEL/LOAEL determination. For example, using the Williams test, the study authors reported a statistically significant difference ($p<0.05$) between MCHC values of 36.6±0.90 and 36.6±0.68 among control and high dose males, respectively, at 13 weeks of age."

Response 5: Because the raw data were not provided, we have had to rely on the statistical results in the CMA 1996 report. We acknowledge the confusing value shown in the male results for 13 weeks, and assumed it was a typo, since statistical significance is claimed without a difference in values or any trend. In the CMA report, the data analyzed using the Williams test are tabulated, and the hematology results– including the MCHC values – are not on that list. Therefore, this comment about the Williams test being inappropriately used may be irrelevant, and the statistical significance of the data as a whole does not seem to us to be an issue.

Comment 6: "OEHHA should carefully review the validity of the biological and statistical significance of the hematological data at the lowest dose. A review of the means and standard deviations at the lowest dose strongly suggests that no meaningful effect on any hematological parameter occurred at the lowest dose. As such, the lowest dose in the CMA (1996) two-generation rat reproductive study is more properly regarded as a NOAEL, rather than a LOAEL. This adjustment would eliminate the need for a 3-fold factor to extrapolate from a LOAEL to a NOAEL; and consequently, the PHG would be raised to 150 ppb."

Response 6: We agree that this is a critical issue, but would rephrase the discussion to question whether the statistical significance of the combined effects at the lowest concentration, 35 ppm, in female pups at day 25 post-partum on hemoglobin, packed cell volume, mean corpuscular volume, and methemoglobin may be toxicologically relevant. It should be noted that these effects at day 25 are substantiated by effects on these same parameters at 70 and 300 ppm, plus significant effects on mean corpuscular hemoglobin and white blood cells, plus effects at 300 ppm only on RBC count and mean corpuscular hemoglobin concentration. Effects at 35 ppm on packed cell volume and mean corpuscular hemoglobin concentration were also observed in both males and females at 13 weeks, according to the data provided. The commenter is asking that all these reported significant effects at 35 ppm be discounted; we disagree that this is the prudent, health-protective approach.

Comment 7: "It is important also to note that the CMA (1996) two-generation rat reproduction study has been reviewed by several regulatory agencies worldwide, and has been employed as the basis for regulatory decisions and guidance. In no instance has the lowest dose (3 mg/kg/day) been interpreted by these agencies as anything other than a NOAEL. Governmental agencies relying on this NOAEL value include:

- **U.S. EPA Office of Water:** NOAEL = 3 mg/kg/day chlorite ion, rounded
- **World Health Organization:** NOAEL of 2.9 mg/kg of body weight per day

• **EPA OPP, Antimicrobials Division (AD):** NOAEL for this study is 2.9 mg/kg/day chlorite

• **EPA Integrated Risk Information System (IRIS):** NOAEL for this study is 3 mg/kg/day chlorite."

Response 7: We are aware of these other interpretations of the data, but disagree that the several significant effects at the lowest dose in the CMA study should be considered a NOAEL. We also note that effects at an even lower dose were found in the rat developmental study of Mobley *et al*. (1990). Although we judged these data to be inadequate to form the basis of the risk assessment (mild, reversible effects; not published in a peer-reviewed journal), they do support the concept of very low-dose effects in neonates, which we are mandated to consider of particular concern (HSC 116365(c)(C)(ii).

Comment 8: "OEHHA should make an adjustment to the exposure assessment for infants to account for the high reactivity of chlorite with infant formula. In our previous submission, the Panel provided OEHHA with a recent study by ERCO Worldwide (Tran, T. V. 2006). This study demonstrated that chlorite ions, at concentrations up to 20,000 ppb, are completely reduced to chloride within 30 minutes of introduction into infant formula. However, OEHHA's Draft Report does not provide for any adjustment for this reduced intake of chlorite because the rate of degradation of chlorite in infant formula is "incompletely characterized."

"While it is true that the U.S. EPA was not able to quantify the reduction of exposure to chlorite in formula during its initial risk assessment, it is also true that the U.S. EPA did take this effect into account when developing the Human Health Risk Management portion of the final RED. While the degradation of chlorite in infant formula could be better characterized and quantified in the future, the fact remains that significant chlorite degradation does occur. The Panel encourages OEHHA to make some adjustment for the degradation of chlorite in formula based on the data currently available. OEHHA should consider the following:

• Baby formula contains ascorbic acid, a compound known to react with chlorite

• Removal of chlorite is not due exclusively to its reaction with ascorbic acid

• Reaction and removal of chlorite in baby formula begins immediately upon preparation

• 30–35% of chlorite is removed within the first 5 minutes

• The reaction accelerates when the formula is warmed to body temperature (in accordance with label directions)."

Response 8: The commenter has provided no additional information to support this claim. We reiterate our earlier position that inadequate data are available to make a specific adjustment for this factor.

Comment 9: "In the event that OEHHA decides that insufficient data exist to adjust for the degradation of chlorite in infant formula, it is strongly recommended that this issue be summarized briefly in the Summary section of the Draft Report. It is likely that

additional information will be published in the future on the interaction of chlorite with the components of infant formula. In keeping with the position stated in the Draft Report, risk managers should be alerted to the possibility that any future drinking water standard should be adjusted to account for the degradation of chlorite in infant formula (to the extent that sufficient data exist to allow for this adjustment). It is important that risk managers be provided the information required to understand the significance of this critical issue."

Response 9: The effect of the chemical reactivity of chlorite on its stability in infant formula, and the added uncertainty for this exposure pathway, has been addressed in the Risk Characterization Section.

Comment 10: "When considered together, the two Panel positions presented in these comments raise the proposed PHG from 50 ppb to approximately 1,000 ppb, as follows:

- Correcting for a NOAEL instead of a LOAEL raises the PHG by a factor of 3.
- Correcting for the removal of chlorite in baby formula raises the PHG by a factor of 7. Taken together: 3 x 7 x 50 ppb = 1,050 ppb.

"…. On the basis of the combination of these two factors, a PHG similar to and consistent with U.S. EPA's MCLG and MCL of 0.8 and 1.0 mg/L, respectively, is scientifically justifiable."

Response 10: OEHHA respectfully disagrees. We do not believe it is prudent to discount the effects at ~3 mg/kg. We concluded they represent a 'mild' adverse effect, and therefore used an uncertainty factor of 3 rather than the default of 10 to extrapolate from a LOAEL to a NOAEL, which seems to us to be consistent with standard practice. We make no correction to the infant exposure value because the data remain inadequate for such a calculation. If adequate data are provided, they can be incorporated into the calculation of a health-protective level at the next scheduled data review.

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