Responses to Major Comments on Technical Support Document

Public Health Goal
For
Bromate
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 bromate, based on the two drafts released for public comment on July 24, 2008 and April 24, 2009. Changes have already been made in response to these comments, and have been incorporated into the version of the document that is 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 (HSC) Section 57003. Development of PHGs for regulated chemicals in drinking water is mandated under HSC 116365. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from Robert R. Hirst, International Bottled Water Association, and Michael A. Dimitriou, International Ozone Association (Sept. 10, 2008)

Comment 1: "We believe the proposed public health goal (PHG) for bromate is premature and does not take into account the difficulty noted by the USEPA, WHO, and other national and global organizations in understanding and detailing with sound scientific methods the true health effects of bromate in the low doses found in drinking water."

Response 1: Development of PHGs is mandated by California HSC 116365 for regulated chemicals in drinking water. The statute also states that if inadequate information is available, the PHG may be set at zero. OEHHA believes that deriving an estimated health risk level for a carcinogen (and other chemicals) is better than setting a goal of zero, which is equivalent to saying that there is no acceptable exposure level. We agree that there is considerable uncertainty in extrapolating a health-risk level for bromate from doses and concentrations used in the available animal studies which have been associated with renal carcinogenicity.

Comment 2: "[T]he risk assessment underlying the PHG does not take into consideration current scientific findings and is therefore overly conservative."

Response 2: As discussed at length in the following comments and responses, OEHHA disagrees with the commenters on the interpretation of available evidence on the toxicity of bromate.

Comment 3: "[T]he proposed PHG is so low that it would decrease the use of ozonation, thus increasing health risks to the public. Fundamentally, we believe that OEHHA's proposal would do more harm than good, as it would have the effect of increasing risks to consumers, not decreasing them. This is because of the very real and scientifically recognized benefits to public health achieved by using ozone as a disinfectant and oxidant for public drinking water supplies and bottled water."

Response 3: OEHHA takes no position on the use of ozonation for disinfection of drinking water. We recognize that disinfectants provide a public health benefit, and are inherently toxic because they are intended to kill microorganisms and viruses; their use represents a risk/benefit calculation. California law restricts us to an evaluation of the human toxic potential of the regulated residual disinfection byproducts in drinking water, which we have provided in the PHG document, without consideration of the net health hazards and benefits of one disinfectant versus another. Such considerations are the purview of the California Department of Public Health and municipal water suppliers.

Comment 4: "[A]s demonstrated by Arie Havelaar et al, … the issue of bromate levels presents a novel "risk-risk" evaluation challenge that should alter the normal risk management process under California law."

Response 4: Under California law (HSC 116365), OEHHA evaluates the risk of individual chemical contaminants in drinking water. It does not manage risk, prepare cost-benefit analyses, nor compare the risk of specific chemical contaminants with the risk of exposure to microorganisms in drinking water. Such comparisons, for risk management purposes, would be carried out by the Department of Public Health Division of Drinking Water and Environmental Management pursuant to setting California Maximum Contaminant Levels for substances in drinking water.

Comment 5: "[T]here is an emerging body of scientific research that shows that low doses of bromate may not even reach the target organs at the levels previously thought."

Response 5: OEHHA has incorporated the available published data into our risk assessment, with appropriate consideration of the effect of variability and uncertainty in the toxicokinetics of bromate, to ensure protection of public health.

Comment 6: "[W]e believe that California needs to completely re-evaluate its approach to this issue and present a new proposal for public comment. At a minimum we recommend that the development of a PHG for bromate should be suspended pending the completion of the new detoxification studies currently underway, in the interest of public health and good science."

Response 6: OEHHA has incorporated the available published scientific data into its PHG document, which we are mandated to develop in a timely manner, according to HSC 116365. The document was made available for two public comment periods, as specified by law.

Comment 7: "In summary, establishing a PHG for bromate at 0.1 ug/l (ppb) would undermine the practical and beneficial uses of ozone in drinking water treatment and bottled water processing. A PHG established at 0.1 ppb would lead water suppliers to an unacceptable alternative, i.e., reducing ozone use, thereby risking incomplete disinfection and increased risk to consumers from increased trihalomethane levels in chlorinated drinking waters and microbiological contaminants in all drinking waters. OEHHA should pause and reconsider its approach to this complex and evolving issue with direct public health consequences."

Response 7: The PHG is not a regulatory document, and does not present any mandate to water suppliers. Choices of disinfectants and their practical application in water disinfection should be informed by all the information available as to comparative risks and benefits of residual disinfection byproducts. The available information will include the public health goals for trihalomethanes that OEHHA is concurrently developing.

Comment 8: "Much research regarding bromate's health effects has occurred over the past decade or more, but a study currently in progress is investigating the fate of bromate from introduction into the stomach, through the liver, and into the bloodstream. … A report on the simulated stomach phase of the project ("The Rate of Bromate Decomposition in the Simulated Human Stomach") was recently released. In summarizing the study's findings, Dr. Cotruvo reports:

> "The issue being investigated was whether bromate could be decomposed to some degree in the stomach (and in other premetabolism segments such as liver and blood), and therefore reduce the amount that could ultimately reach target organs. If sufficient bromate could be reduced prior to reaching target organs, the actual risk at low environmentally relevant doses would be lower than predicted by the current risk calculation methodologies.
>
> "Our prior studies had shown that hydrogen sulfide is present in stomach acid, and the half-life of decomposition of bromate in acid and ~10^{-4} molar hydrogen sulfide and some thiols was on the order of 2 minutes at pH 0.8. This half-life is biologically relevant in terms of retention time in the stomach of ingested water or food. The reaction is very sensitive to the acidity (much more rapid at low pH). There are also other components in the stomach that are more reactive than HCl; these include thiol-containing proteins, and especially hydrogen sulfide that was quantified in a sample of human gastric juice that was analyzed.""

Response 8: The pharmacokinetic studies (Keith *et al.*, 2006; Cotruvo Associates, 2005) cited in the above comment are chemical assays measuring reduction of bromate in real and synthetic gastric juices and simulated human stomach. Keith *et al.* (2006) calculated average half-lives of bromate reduction as 144 min (124 to 164 min) in real human gastric juice and 90 min in synthetic gastric juice. Overall, the half-life of bromate reduction ranged from 2 to 454 min in solutions containing various concentrations of hydrogen sulfide and acidity, and varied between trials. Despite this large range in half-lives of bromate reduction, Keith *et al.* (2006) concluded that as much as 99 percent of the bromate ion should be reduced *in vivo* during its residence in the stomach. The report stated that this is "a clear indication that the chemistry of bromate ion in gastric juice is a complex process and for a complete mechanistic understanding, additional experiments will be needed."

Wang and coworkers (2001) reported half-times of stomach emptying as approximately 15 min for liquid and less than two hours for a solid in rats, irrespective of the fasting condition. Gastric emptying half-time for liquids in fasted human subjects is about 10 to 20 minutes (Chaudhuri, 1974; Umenai *et al*., 2008), but the half-time can increase to two or three hours with meals, depending on the meal content and volume (Siegel *et al.*, 1988; Urbain *et al*., 1989; Chew *et al*., 2003). These variable gastric emptying times suggest to us that accepting the conclusion of Keith *et al.* (2006) that as much as 99 percent of the bromate ion should be reduced during its residence in stomach would be a great oversimplification, and inadequately health-protective.

To address the pharmacokinetic properties of bromate, OEHHA included additional discussions in the PHG on the gastrointestinal uptake of bromate and disposition in target tissues (Fujii *et al.*, 1984; Delker *et al.*, 2006). Further *in vivo* pharmacokinetic studies

would reduce uncertainties in absorption and metabolism of bromate in both animals and humans. In the absence of human data on the kinetics and chronic toxicity of bromate, health-protective levels are estimated from animal experimental data.

Comment 9: *Excerpts were provided for guidance to the PHG development from an international expert workshop funded by the American Water Works Association Research Foundation on dose-response of bromate published in Toxicology 221, 17 April, 2006.*

Response 9: As recommended, OEHHA re-examined the special issue in Toxicology and incorporated additional studies (Delker *et al.*, 2006; Umemura and Kurokawa, 2006; Bull and Cotruvo, 2006) into the bromate PHG. To strengthen the discussion on genotoxicity and mode of action, OEHHA also included additional genotoxicity studies and review articles (Kurokawa *et al.*, 1984, 1985, 1987; Ballmaier and Epe, 2006; Kawanishi and Murata, 2006; Kaya and Topaktas, 2007; Luan *et al.*, 2007).

Comment 10: *From Bull and Cotruvo (2006):* "In the case of male rat kidney tumors, the accumulation of α-2_{μ}-globulin in the kidney appears to have contributed to the cancer response at low doses. ... The accumulation of α-2_{μ}-globulin is an effect that is specific to the male rat and does impart a tumor promoting mechanism not seen in other species, not even female rats (Swenberg and Lehman-McKeeman, 1999). Using the male rat kidney tumor response generated by this mechanism in quantitative risk assessments would result in an over estimate of the apparent carcinogenic risk to humans."

"There are remarkable species differences in the tumorigenic response to bromate, with mice and hamsters being 1/5 and $1/50^{th}$ as susceptible (as the rat) to kidney cancer induced by bromate (Gold, 2005)."

Response 10: Bull and Cotruvo (2006) suggested that bromate caused renal tumorigenesis via a molecular mechanism associated with α_{2u}-globulin-induced nephropathy, which occurs exclusively in male rats and is not predictive of risk to humans. They recommended that further studies be focused on the female rat. However, in order to elucidate species differences in kidney carcinogenesis, an IARC international workshop in 1997 outlined criteria (all of which must be met) for establishing the exclusive role of α_{2u}-globulin associated nephropathy with renal carcinogenesis in male rat (IARC, 1999). The following is a partial list of essential evidence:

- tumors occur only in male rats
- absence of hyaline droplets and other histopathological changes in female rats and mice
- reversible binding of chemical to α_{2u}-globulin
- negative for genotoxicity or mutagenicity of the chemical, with increased cell proliferation due to nephropathy

OEHHA determines that an exclusive role of α_{2u}-globulin-induced nephropathy for renal carcinogenesis in potassium bromate-treated male rats cannot be established, because of the following observations:

- Potassium bromate causes renal tumors in both sexes of rats as well as in mice (DeAngelo *et al.*, 1998; Kurokawa *et al.*, 1983, 1984, 1990).
- Potassium bromate exposure via drinking water enhanced proliferation in proximal convoluted tubular cells and caused accumulation of hyaline droplet-like material and basophilic alteration in proximal tubules in kidney of female rats (Umemura *et al.*, 2004). Oral administration of sodium or potassium bromate was also associated with renal cell proliferative changes in female Sprague-Dawley rats (NTP, 2001) and dermal exposure to sodium bromate resulted in nephropathy in both male and female Tg.AC hemizygous mice (NTP, 2007).
- A stable ligand-protein complex formation between a chemical and α_{2u}-globulin protein has been shown to be a critical step for the α_{2u}-globulin-mediated nephropathy and carcinogenesis. Ligands must be hydrophobic to fit the α_{2u}-globulin binding site. Bromate, being a negative charged molecule, probably is not a good candidate to create a stable complex with the α_{2u}-globulin protein molecule. No data are currently available to support the binding of bromate to α_{2u}-globulin protein and subsequent reduction in proteolytic degradation of the bound protein.
- Genotoxic activity of bromate has been demonstrated in several *in vitro* bioassays.
- There is significant evidence for other modes of action (MOA) such as oxidative DNA damage and a sulfhydryl-mediated DNA oxidation (Umemura *et al.*, 2004; Delker *et al.*, 2006).
- Potassium bromate causes a dose-dependent increase in incidence of tumors at multiple sites (renal cell, thyroid, and mesothelioma) in male rats, further supporting the contribution of additional MOA(s) to carcinogenesis in male rats.

IARC (1999) concluded, "In the absence of data on binding of bromate to α_{2u}-globulin and demonstration of consequent reduced proteolytic degradation of the bound protein, it is not possible to determine whether α_{2u}-globulin accumulation resulted from the α_{2u}-globulin mechanism described above or perhaps resulted from oxidative damage associated with $KBrO_3$ treatment … it is likely that α_{2u}-globulin accumulation was irrelevant to the carcinogenic effects of $KBrO_3$ in the kidney." Based on the above, OEHHA believes that there is insufficient evidence to conclude that α_{2u}-globulin accumulation is responsible for the renal carcinogenesis in male rats, and that it is therefore appropriate to develop a PHG for bromate using a multistage-in-dose Weibull-in-time model on the male rat data from DeAngelo *et al.* (1998).

Comment 11: *Defending the use of ozone for drinking water disinfection, the Bull and Cotruvo (2006) workshop commented:* "If bromate in finished water is found to pose risks of the magnitude estimated using default assumptions, it may ultimately preclude [use of ozonation] in some locations, or at least require the introduction of significantly

higher cost treatment technologies. … The main concern is that with the improvement of analytical techniques, the lack of dose-response information on key toxicological endpoints, and insertion of additional uncertainty factors for lack of information on specific life stages, could drive regulatory agencies toward unnecessarily stricter limits in the interest of conservatism."

Response 11: OEHHA understands the benefit of ozonation of drinking water. However, the goal of developing PHGs for regulated contaminants in drinking water is to provide a scientific-based risk assessment of each of the contaminants. This will allow the Department of Public Health to conduct cost/benefit analyses of the various treatment alternatives to help derive the MCL for bromate.

Comment 12: *The commenters emphasize the following passage from the Bull and Cotruvo (2006) workshop:* "It is quite likely that the relationships between external dose [of bromate] and dose at target sites will have a non-linear character at lower doses, because of a variety of variables including pre-systemic degradation, the potential involvement of anion carriers in its distribution, and the potential for secondary mechanisms that may become apparent if tissue thiol levels become depleted by high bromate doses."

Response 12: OEHHA agrees that multiple mechanisms of interaction of bromate with endogenous molecules are likely to result in complex dose-response relationships. However, this is true for all reactive chemicals, and the default cancer risk estimation methods are nevertheless applied until the applicability of better models can be established for the particular case. We look forward to reviewing the physiologically based pharmacokinetic (PBPK) modeling results when they become available.

Comment 13: *The commenters state that research studies currently underway, scheduled to be reported on in December 2010, will make a significant contribution to understanding bromate pharmacokinetics, which will need to be incorporated into the bromate risk assessment.*

Response 13: We look forward to reviewing the new data during our next bromate review process.

Comment 14: "Ozone is a Necessary and Beneficial Barrier Against Halogenated Disinfection By-products and Microbial Risk. … Public water systems and the bottled water industry are very conscious of the potential for bromate to be produced as a by-product of the disinfection process, and have developed strategies to minimize bromate levels. However, our experience to date has shown that reducing bromate levels below the level proposed by OEHHA is simply not consistently practical or feasible. In addition, it should be recognized that a very low PHG would also have a serious adverse impact on the use of chlorine and hypochlorite in water treatment. … We understand that adoption of the PHG does not force changes in drinking water treatment, but it will effectively influence water suppliers to reduce or avoid use of ozone. We believe that

this is a counterproductive and unacceptable option to attempt compliance with future maximum contaminant levels for bromate at or near the proposed PHG."

Response 14: It is beyond the scope of the PHG process to incorporate risk management decisions or consider these decisions in calculation of health-protective concentrations of regulated contaminants in drinking water. The chemical toxicity, beneficial uses of ozonation disinfection, and other technical aspects will be carefully considered by the California Department of Public Health in their regulatory processes.

Comment 15: "The proposed PHG is very conservative for many reasons. While many decisions underlying the proposed PHG are made as a matter of policy and explained in the "fine print" of the document, it is important that readers who are not well-versed in the intricacies of cancer risk assessment understand the implications. The risk statements on page 28 do not adequately communicate the health-conservative nature of the estimated PHG and imply a level of certainty that does not exist. For example, the PHG is described as "the estimated drinking water concentration corresponding to a one in one million" risk factor. Similarly, "Risks of 10^{-5} and 10^{-4} are associated with lifetime exposure to concentrations of 1 ppb and 10 ppb, respectively." These numerical 'risk' values would be much more logically treated as index values rather than estimates of actual cancer risk.

Response 15: OEHHA agrees that the PHG calculation includes several health-protective assumptions, and attempts to explain them in the discussion in this and every PHG document. The 10^{-6} cancer risk estimate is a theoretical value, based on standard extrapolation methods, and certainly may be thought of as an index value, to be used in comparison with similarly-derived values for other contaminants in risk/benefit calculations.

Comment 16: "In respect to the exposure assumption, the proposed PHG is based on an assumption that 3.08 L of water per day (the 95^{th} percentile value from a survey) is consumed daily for 70 years. In contrast, the traditional default daily drinking water consumption value used by U.S. EPA and WHO is 2 liters per day. The US total water mean value was 1,241 l/d and the 90^{th} percentile was 2.345, and 95^{th} percentile was 2.992 (Ershow and Cantor, 1991). Even applying the 95^{th} percentile on a spot basis, a person is highly unlikely to drink 3.08 L of water per day for 70 years, as assumed in the derivation of the PHG. Further, by assuming 3.08 L of daily water consumption (95^{th} percentile upper bound) every day for 70 years, the PHG poses a theoretical/hypothetical one-in-a-million risk only for those few individuals at the 95^{th} percentile. The 95% of the population consuming less than 3.08 L per day of water would have less than a one-in-a-million risk and the average population risk would be less than one-in-a-million."

Response 16: The U.S. EPA's recent evaluation of drinking water intake rates used data from the Continuing Survey of Food Intakes of Individuals, a nationally representative survey of over 20,000 people from all 50 states (U.S. EPA, 2004). This analysis shows dramatic differences in drinking water rates across population subgroups. Based on these data, it appears that the traditional drinking water default values (2 liters per day for adult

and 1 liter per day for child) may be inadequately protective of most population groups, especially for young children and lactating women. For this PHG calculation, OEHHA utilized the upper 95th percentile of municipal water consumption for the general population, 0.044 L/kg-day, from this U.S. EPA analysis to ensure that high-end water consumers are accounted for. This new default value is an age-adjusted daily drinking water consumption rate, which is more appropriate for life-time exposure estimates. Use of the upper 95th percentile value helps ensure protection of the entire population. We agree that the average risk is less.

Comment 17: "The combination of using these two upper 95th percentile values means that the PHG could not represent a risk as high as one-in-a-million risk for the general population of California. The best theoretical/hypothetical estimate of a one-in-a-million risk would be much higher (perhaps 10 times higher) than the proposed PHG. In other words, it is just as likely, for example, that 0.1 ppb (the proposed PHG) represents a one-in-ten-million risk (10^{-7}) or lower."

Response 17: We agree that the PHG calculation includes these health-protective aspects, and believe that the discussion has adequately characterized the uncertainties and assumptions in the methods used.

Comment 18: "The use of ozone to disinfect drinking water reduces exposure to halogenated disinfection by-products in drinking water. OEHHA has raised concerns about the potential carcinogenicity of trihalomethanes, and chloroform is identified on the Proposition 65 list as a chemical "known to cause cancer", which is no longer correct with respect to drinking water. In addition to estimating the hypothetical cancer risk from the formation of bromate from ozonation of drinking water, OEHHA should estimate the theoretical/hypothetical reduction in cancer risk from the reduced exposure to disinfection by-products due to ozonation of drinking water."

Response 18: That would be a very interesting project, but is well beyond the scope of the development of a PHG for bromate. Chloroform is clearly a carcinogenic compound; the carcinogenic dose-response is disputed, just as it is for bromate.

Comment 19: "To sum up, the proposed PHG is a very conservative estimate of what level of bromate in drinking water represents a theoretical/hypothetical one in a million risk. OEHHA should re-visit whether some of the underlying assumptions are overly conservative. At the least, it is critical that the PHG document accurately convey to readers (including non-scientists) the appropriate interpretations of policy-driven choices underlying the proposed PHG, and that these numerical constructs do not represent actuarial cancer risk or cancer cases, but are more like relative potency indices that are still burdened by the well known scientific uncertainties of these types of low dose calculations. Also, the lower bound risk could be zero. It is especially important for OEHHA to clearly communicate this information to risk managers who will have to carefully consider and balance the potential risks of carcinogenicity and the public health benefits of making our drinking water safe from infectious agents."

Response 19: In the final PHG document posted on the OEHHA website, we have endeavored to convey the available information about bromate toxicity as clearly and concisely as possible, for many of these reasons.

Comment 20: "In conclusion, we strongly urge OEHHA to re-evaluate its risk management approach to the issue of bromate in water. The current proposal would do more harm than good, as it would have the unintended consequence of *increasing* the risk to consumers from microbial hazards both in public drinking water supplies and bottled water. This result is not in the interest of public health. OEHHA should also reconsider the applicability of its very conservative chronic risk evaluation methodology in this circumstance, especially in light of emerging research that suggests less bromate may reach target organs than previously thought. Therefore, because of the significant mechanistic and low dose metabolism data that are being developed, we believe it is in yours and the public's best interest that the development of a PHG for bromate should be suspended pending the completion of the new metabolism and detoxification studies currently underway, in the interest of public health and good science. This suspension would allow you to incorporate the current state-of-the-science as well as the soon to appear PBPK results."

Response 20: As previously discussed, the Department of Public Health is responsible for the risk management of drinking water contaminants. Health and Safety Code Section 116365 requires OEHHA to conduct risk assessments of drinking water contaminants and develop non-regulatory PHGs that the Department of Public Health uses as guidance in its risk management activities. In regulating California's publicly supplied drinking water, the Department considers the costs, risks and benefits associated with the treatment of drinking water. In contrast, OEHHA can only consider health data on the toxicity of drinking water contaminants when developing PHGs. State law does not allow PHGs to reflect the kind of risk-benefit analyses cited by the commenter.

OEHHA believes that there is adequate evidence on uptake and deposition of bromate in target tissues, genotoxic effects of bromate in various *in vivo* and *in vitro* systems, well designed animal studies from multiple research groups, and tumors at multiple sites in multiple species and sexes to conduct a risk assessment for bromate in drinking water. Based on the currently available data, we believe that the PHG is sufficient to protect the public, including sensitive subpopulations, from significant adverse effects resulting from exposure to bromate in drinking water. OEHHA is aware of the uncertainties in our risk assessment, as well as the ongoing research studies and the development of a PBPK model for bromate. We have included additional discussions on uncertainty of the risk assessment in the PHG document. With the availability of new data in the future, the risk assessment for bromate can be further improved.

Comments from David A. Smith, Resident of Arizona

Comment 1: "http://ntp.niehs.nih.gov/index.cfm?objectid=BDC199B6-123F-7908-7BEBC128F6C1ABBE... *sodium bromate* tested to 800 mg/L for almost a year, and no carcinogenicity found."

Response 1: The reference is to chronic *in vivo* studies involving oral or dermal exposure of genetically modified mice to sodium bromate for 29 to 43 weeks (NTP, 2007). These studies were part of an initiative to evaluate the use of transgenic animal models for detecting the carcinogenesis of disinfection byproducts and other environmental contaminants. NTP (2007) concluded, "These studies provide evidence that these transgenic mouse models are not a sensitive and rapid means of assessing potential toxicity and carcinogenicity of sodium bromate." OEHHA considered results from these genetically modified mice not directly applicable for PHG calculation because of the less-than-lifetime exposure periods and the uncertain effect of the genetic modifications. Thus the carcinogenesis outcomes from these animals cannot be correlated directly or extrapolated to wild-type animals or humans.

Comment 2: "All researchers look at postassium bromate, because they know cancer is the result. Just as it is with potassium carbonate. But no one legislates carbonate (aka. hardness). The problem is with excesses of potassium and the "-ate", meaning excess oxygen. And this only for certain species.

"Where mutagencity is tested against single cells, both sodium bromate and potassium bromate show carcinogenic behavior. As do table salt and ethanol. Single cells respond to changes in pH by mutating. When testing, the researchers do not maintain constant numbers of sodium or potassium ion. This means the cells will suffer a change in internal pH when the cell's exterior is flooded with extra Na+ or K+ ions. This requires the internally regulated Na+/K+ ATPase pump to compensate for the sudden change in ions... which it does after internal pH changes.

Additonally, a dose response curve has been established for potassium bromate, which was not available when the US-EPA made their dispensation."

Response 2: Genotoxicity studies in rats (Umemura *et al.*, 2004) revealed elevated 8-oxodG levels in kidney of potassium bromate-treated animals. These results suggested oxidative stress as a potential mechanism of action for renal carcinogenesis in rats. Although oxidizing agents can induce oxidative stress in biological systems, not all "-ate" chemicals carry the same activity. Potassium bromate is known as a powerful oxidant with a redox potential of 1.44 V in acidic media (Singh *et al*. 1989), but potassium carbonate is not generally considered as an oxidizing agent. Neither potassium nor sodium carbonate is considered a carcinogen. Very high doses of potassium bicarbonate were reported to cause bladder but not renal tumors, presumably related to a chronic pH imbalance, while potassium chloride (a neutral salt), had no effect at a similar chronic dose (Lina and Kuijpers, 2004).

In a two-stage *in vivo* renal tumorigenesis study, Kurokawa and associates (1985) used N-ethyl-N-hydroxyethylnitrosamine (EHEN) as a tumor initiator to investigate the promoting activity of potassium bromate on renal tumorigenesis in male F344 rats.

Histopathological changes in kidney including significant increases in dysplastic foci density and renal cell tumor density were reported in EHEN/potassium bromate-treated animals compared to the EHEN/distilled water group. These *in vivo* data suggested the cancer promoting activity of potassium bromate in renal tumorigenesis initiated by EHEN. More importantly, potassium bromide showed no promoting activity under the same experimental conditions, even at much higher concentrations. For these and other reasons, OEHHA does not concur with the comment that potassium bromate induces mutagenesis in cultured cells via perturbation of the Na^+/K^+ ATPase pump by the extra K^+ ions. These *in vivo* studies demonstrated the carcinogenicity of potassium bromate in whole animals with oxidative stress as one of the potential MOAs and supported the development of the PHG for bromate from the study of DeAngelo *et al.* (1998).

Comments from Robert R. Hirst, International Bottled Water Association (IBWA, and Michael A. Dimitriou, International Ozone Association (IOA) (May 28, 2009)

Comment 1: "IBWA and IOA submitted fairly detailed comments on the July, 2008 draft public health goal (PHG) for bromate on September 10, 2008. We hereby reiterate those comments, which are still valid and provide these additional comments on the revised draft bromated PHG from May, 2009."

Response 1: Responses to the previous comments are addressed above. Here, OEHHA focuses on the new comments.

Comment 2: "Although the revised draft PHG includes mention of several of the citations ... it essentially disregards their substance and content. Simply mentioning a comment or publication without addressing its relevance to the risk assessment decision does not constitute adequately addressing comments in a legally driven decision process. It is important that such a decision would not be considered arbitrary and capricious, and without a rational basis."

Response 2: OEHHA agrees with the commenters that risk assessment decisions should not be "arbitrary and capricious, and without a rational basis." In preparation of a PHG, OEHHA reviews all available and published scientific literature. Toxicological studies summarized in the bromate document are those directly relevant to the risk assessment for human exposure to bromate in drinking water. OEHHA has reviewed the studies recommended by the commenters. Although these articles contain detailed discussions on bromate toxicity or hypotheses for future research studies, most of them are reviews and do not contain new data that would warrant an alternate PHG calculation. OEHHA has included the relevant discussions in the revised PHG and concludes that the PHG calculation is appropriate for assessing the risks of human exposure to bromate in drinking water.

Comment 3: "The published conclusions of the bromate expert workshop supported by the 18 publications in the Toxicology, 2006 special issue was that the shape of the dose

response at low doses was below linear, and that led to the need of OEHHA reexamining the methodology and default assumptions utilized in the cancer risk assessment."

Response 3: OEHHA thoroughly reviewed the 18 articles referenced above and revised the draft bromate PHG accordingly. These 18 publications discuss potential modes of action for bromate carcinogenesis, as well as potential *in vivo* activation and detoxification pathways of bromate. However, they do not contain sufficient data to support a non-linear dose response at low doses of bromate. Additionally, OEHHA carefully considered results from other studies—the *in vivo* and *in vitro* data that demonstrated mutagenicity of bromate (C.I.R., 1994; Morgan *et al.*, 2002 ; Umemura *et al.*, 2004); recent evidence on distribution of bromate to target organs (Delker *et al.*, 2006); and tumors at multiple sites in both sexes of rats and in male mice, reported by independent laboratories (Kurokawa *et al.*, 1983; DeAngelo *et al.*, 1998; DeAngelo, 2006).

OEHHA does utilize science policy-based default options, including absence of a threshold in the dose-response curve, unless specific data are available to indicate otherwise (U.S. EPA, 2005; OEHHA, 2009). Currently, specific toxicokinetic data for bromate at low doses and direct evidence related to threshold carcinogenic effects of bromate are lacking in the literature. OEHHA determines that there are insufficient tumorigenicity data to define the shape of a full dose-response curve or to support detailed mechanistic modeling for the cancer risk assessment of bromate. Although complex MOAs of bromate may lead to a non-linear dose-response curve at low doses (or a toxicity threshold) for individuals, variations within the human population often smooth the dose-response curve and result in a linear dose response at low doses (White *et al.*, 2009). Taken together, application of a default low-dose linear cancer risk assessment for the proposed bromate PHG is appropriate for protection of public health.

Comment 4: "We also provided additional information relative to decomposition to reinforce the expert committee consensus. At this time we provide additional supporting information that further demonstrates that the dose response in the lower range is likely below linear. It is abundantly clear that the default linear assumption is invalid and it will lead to an incorrect and over estimation of the hypothetical low dose risks."

Response 4: OEHHA has included review of the *in vitro* synthetic gastric juice data from Keith *et al.* (2006) in the PHG document. OEHHA appreciates the submission of a current research report by the commenters. After publication in a peer-reviewed journal, the new data will be considered in the future re-evaluation of the bromate PHG. Based on all the currently available published information, OEHHA determines that there is insufficient information to support a threshold cancer effect of bromate. OEHHA understands that a default linear extrapolation from low doses may lead to a conservative cancer risk assessment for bromate, but this default assumption is appropriate for the protection of public health.

Comment 5: "Thus, we respectfully request that you delay issuance of a bromate PHG pending receipt and examination of the latest detoxification metabolism information and

the Physiologically Based Pharmacokinetic Model, and revised risk assessment being generated by the work of JA Cotruvo, RJ Bull, J Fisher, B Cummings, CN Ong, O Quinones and S Snyder in the AWWARF 4042 project that is well underway with the title: Low Dose Risks from Bromate: The Relationship between Drinking Water Concentrations and Actual Dose to Susceptible Organs in Rats and Humans."

Response 5: The bromate PHG has been prepared based on all the currently available published data. State law recognizes that new information on drinking water contaminants will become available, and for this reason requires OEHHA to periodically review each PHG. Advances in bromate research will benefit the re-evaluation of the chemical in the future.

Comment 6: "Summary statement: "Bromate has a long history of use as a food additive of up to 75 ppm in flour; it is largely converted to bromide in the baking process."

It is imperative that you carry out an assessment to determine the extent of the residual bromate presence in baked goods that may still utilize bromated flour, and also a relative source contribution (RSC) calculation. As far as is known, this is the only potential significant non-drinking water ingestion source of exposure to the general population. What is the relative exposure and hypothetical risk from that dietary exposure source in the population? This is relevant to both the cancer and non cancer calculations."

Response 6: OEHHA cannot identify adequate scientific information on intake of bromate from bakery products or other dietary sources to determine the relative exposure and hypothetical risk from dietary exposure to bromate. Evaluation of cancer risk from exposure to bromate from other dietary sources is beyond the scope of the PHG. The estimation of cancer risk of chemicals for PHG calculation is determined solely for exposure from drinking water, as "extra risk" from this source.

In the absence of adequate relative exposure data, a default 20 percent RSC for drinking water has been applied in the non-cancer risk calculation, although this does not affect the final PHG, because the PHG is based on the lower cancer value.

Comment 7: "Perhaps bakers should be listing bromate as a product component if they do not already?"

Response 7: OEHHA concurs with the comment. OEHHA has listed bromate as a cancer-causing chemical under Proposition 65 (OEHHA, 2001, 2008b). As a result (under California Code of Regulations Title 27.4.1, Article 6 and California Health and Safety Code, Division 20, § 25249.6 (OEHHA, 2008a; HSC, 2009)), businesses must provide a Proposition 65 warning for any products (including bakery goods) that cause exposures to bromate above the no-significant risk level.

Comment 8: "Statement: 'Bromate was shown to be mutagenic in *in vitro* and *in vivo* studies.' The statement is correct, but the draft PHG fails to indicate its relevance to the human risk assessment at low doses. The Moore and Chen paper from the Toxicology 2006 monograph that we brought to your attention states, 'While it is clear that bromate

can cause damage in the target tissue, it is not clear whether bromate is a mutagenic carcinogen, that is, whether the observed tumors result from a mutagenic mode of action.' Of course, that begs the question of whether ingested bromate survives to reach a target tissue at low doses."

Response 8: Although there are no direct data to support or exclude a direct mutagenic action of bromate at target sites, positive results from genetic toxicity bioassays *in vivo* and *in vitro*, toxicokinetic data demonstrating distribution of bromate to target organs, and direct correlation between bromate exposure and tumors at multiple sites in two species strongly support the carcinogenesis of bromate in laboratory animals. Bromate alters gene expression *in vitro* (Morgan *et al.*, 2002), induces kidney 8-oxodG level *in vivo* (evidence for DNA oxidation) (Umemura *et al.*, 2004), and causes DNA breakage *in vitro* (Ballmaier and Epe, 2006). The Kurokawa and associates (1985) report of tumor promoting activity of bromate in the presence of N-ethyl-N-hydroxyethylnitrosamine (a tumor initiator) further demonstrates complicated MOAs in bromate carcinogenesis. Based on these findings, it is reasonable to believe that bromate is a potential human mutagen at low doses, unless sufficient data prove otherwise. Recent results from a radioisotope study by Delker *et al.* (2006) support the distribution of bromate to target sites in rats. Taken together, it is reasonable to believe that bromate induces carcinogenesis in animals via mutagenic activity. OEHHA agrees that future studies on toxicokinetic properties of bromate will reduce uncertainties in the risk assessment of bromate and improve the calculation of health-protective concentrations.

Comment 9: "Statement: 'It is noteworthy that the contention that bromate is rapidly degraded is challenged by Kutom et al. (1990), inferring from data from several sources that 'Bromates are very stable in the body and only small quantities are reduced to the less toxic bromide ion.'"

Actually it is NOT noteworthy. It is obvious from several studies including the current *in vivo* rat and *in vitro* human blood kinetics studies using low doses and sensitive analytic techniques not available in 1990, that the Kutom et al 1990-related statement is incorrect, and certainly at less than bioassay doses."

Response 9: Recent results from an *in vivo* radioisotope study in rat conducted by Delker and associates (2006) suggest a dose-dependent distribution of low-dose bromate (as low as 25 μg/kg or 0.25 mg/L) to target organs. OEHHA has included additional discussion of this radioisotope study in the PHG document. Further *in vivo* toxicokinetic studies should reduce uncertainties in estimation of absorption and metabolism of bromate in both animals and humans.

Comment 10: "Statement: 'Potassium bromate is more highly toxic than sodium bromate…' This is based upon LD_{50} data in the hundreds of mg/kg. Even if it is correct, it is irrelevant to the low dose risk issues."

Response 10: The PHG document covers acute, subchronic, and chronic toxicity of bromate in both animals and humans. The above statement is directed to acute toxicity of bromate and is noted in the corresponding section of the PHG. The purpose of this

statement is to justify the choice of using potassium bromate by researchers in most of the toxicity studies found in literature. OEHHA concurs with the commenters that observations on high-dose acute toxicity often are not applicable to low-dose chronic toxicity. In fact, OEHHA believes that sodium bromate and potassium bromate elicit their toxicity in the form of anionic bromate, especially at low doses. Therefore, the proposed PHG—even though it is derived from potassium bromate—is recommended for all sources of bromate in drinking water.

Comment 11: "Statement: 'Umemura and Kurokawa concluded that mechanisms for cancer induced in male rats were more complex than in female rats.'

We agree and this raises the issue of the consequences of hyaline droplet formation and α2u-related cytotoxicity tumors that are unique to male rats, and their contribution to the incidence of kidney tumors, which would cause a greater calculated risk, even though those tumors are not relevant to human risk calculations. This has been shown in several studies (Umemura et al, 1993; Umemura et al, 1998; Umemura et al, 2004; Umemura and Kurokawa, 2006) which are described in the Toxicology, 2006 monograph. We do not understand why OEHHA ignored those studies, which cast serious doubt on the uncritical use of all of the kidney tumors from the male rat bioassay in the draft quantitative risk assessment. Including all of the male rat kidney tumors inflates the projected human risk."

Response 11: OEHHA has concluded that there is insufficient evidence to establish an exclusive role of α_{2u}-globulin in bromate-mediated renal tumorigenesis in male rats. Considering the mutagenic activity of bromate, occurrence of tumors at multiple sites in male rats, and tumors in both sexes of rats and in male mice, multiple carcinogenic MOAs are possible. However, there is no way to distinguish among the various possible causes of tumors in any particular organ. Therefore, in accordance with cancer guidelines, OEHHA has used the most sensitive species and sex, with the combined incidence of multi-site tumors, to estimate possible human cancer potency. OEHHA believes that developing a PHG for bromate using a multistage-in-dose Weibull-in-time model with the multi-site tumor data in the male rat study from DeAngelo *et al.* (1998) is appropriate.

Comment 12: "Statement from Kurokawa et al 1987: 'The authors concluded that a higher dose of potassium bromate within a shorter period of time was more effective than a lower dose over a longer period.' We agree, and this reinforces the concept that bromate is significantly metabolized at lower doses, so the dose response at lower doses is likely not linear."

Response 12: The statement from Kurokawa *et al.* (1987) refers to two very high bromate doses in a chronic rat study—approximately 16 and 32 mg/kg-day of bromate. These two doses were similar to the two highest doses (12.9 and 28.7 mg/kg-day bromate) in the rat study of DeAngelo and associates (1998). This statement does not apply to the shape of the dose-response curve at low bromate doses. The highest dose of bromate may trigger additional toxicological pathways that could lead to tumors.

Conversely, lower doses of bromate may involve a dominant MOA at a target site, which results in an essentially linear dose-response curve for that effect and dose range. The data available, including that in the DeAngelo study (1998), at doses of 1.2 to 28.7 mg/kg-day, cannot establish the validity of any non-linear, threshold mechanism. Therefore the cancer risk was estimated from low-dose extrapolation assuming linearity at low doses.

Comment 13: "Statement: 'The NTP (2007) studies using non-standard transgenic mouse models did not report any neoplastic effects from sodium bromate.'

We would interpret that statement to mean that the transgenic mice were not more susceptible than normal mice to bromate toxicity, indicating that at reasonable doses more fundamental matters of metabolic detoxification may be more controlling than genetics. It is well known that the mouse and hamster are much less sensitive than the male rat to bromate induced high dose tumors (Gold, 2005). Whether the male rat is the appropriate animal model to use for human risk projection is a serious scientific and risk assessment question that should be resolved with factual data before an extrapolation is made."

Response 13: As stated in the PHG document, this NTP study (2007) was part of a method development initiative on using transgenic animal models for detecting the carcinogenesis of disinfection byproducts and other environmental contaminants. NTP (2007) concluded, "These studies provide evidence that these transgenic mouse models are not a sensitive and rapid means of assessing potential toxicity and carcinogenicity of sodium bromate." OEHHA considered results from these genetically modified mice not directly applicable for PHG calculation because of the less-than-lifetime exposure periods and the uncertain effect of the genetic modifications. Thus the carcinogenesis outcomes from these animals cannot be correlated directly with or extrapolated to wild-type animals or humans.

OEHHA believes that there is insufficient evidence to support the commenters' hypothesis that "metabolic detoxification may be more controlling than genetics." In addition, cancer guidelines support the use of the most sensitive species, strain, sex, and tumor site in estimating human cancer risk, except for cases in which such tumors are clearly not relevant to humans. That does not appear to be the case for liver tumors induced by bromate in male rats.

Comment 14: "Non cancer effects. The OEHHA calculation of the public health protective concentration C is flawed in several respects and the resulting logic conflicts with the cancer risk and PHG logic… The draft C value contains overlapping uncertainty factors. The UF of 100 is intended to account for the higher risk population. However, OEHHA also utilizes the 95th percentile water consumption which additionally decreases the C by about 1/3, and the default RSC of 0.2 is effectively an additional UF of 5. The RSC assumption leads to an implicit potential non-drinking water exposure of up to 620 µg per day. If that were even remotely valid it would render the draft cancer-based PHG of 0.1 µg per liter to be irrelevant and a waste of public money to promulgate. It is

essential for the internal logic of the PHG that OEHHA utilizes an appropriate aggregate UF and determines a plausible RSC."

Response 14: In calculating a non-cancer PHG, an uncertainty factor (UF) of 10 is applied to address variation between rats and humans and another UF of 10 to cover variation in susceptibility within the human population. OEHHA utilized the upper 95th percentile of municipal water consumption for the general population, 0.044 L/kg-day to ensure that high-end water consumers are accounted for. These three factors address different uncertainties and variabilities in the risk assessment. OEHHA is unable to identify sufficient data to derive a chemical-specific RSC for bromate and therefore applied a default RSC of 0.2. Based only on non-cancer effects, a total exposure to 770 µg/day would be considered acceptable, and the portion derived from drinking water at 50 µg/L corresponds to 20 percent of that value. However, the non-cancer evaluation does not represent any presumption that the other sources actually provide up to 620 µg/day of bromate, as proposed by the commenters. Comparing the assumed other source value to the bromate consumption from water to protect against cancer is irrelevant.

OEHHA agrees that the PHG calculation includes several health-protective assumptions and the average risk is less. OEHHA believes that the PHG document has adequately characterized the uncertainties and assumptions in the methods used.

Comment 15: "In the PHG risk characterization, it is acknowledged that there is significant uncertainty on the bioavailability of bromate in humans based upon the lack of information on the pharmacokinetics in humans. It goes on to encourage development of a PBPK model to provide a better understanding of the pharmacokinetics and toxicity of the chemical and further improve the risk assessment. We are pleased to report that it is our understanding (IO_3A, 2009) that much metabolic data collection in the rat and also *in vitro* studies in human blood have been generated, new kinetics data are becoming available, additional studies are in progress, and that development of both the PBPK model and a revised risk assessment are well underway."

Response 15: It is encouraging to learn that ongoing research aims to delineate the toxicokinetic properties of bromate in animals and humans. However, the PHG has been developed based on all currently available published data. OEHHA will incorporate relevant new published data in the next re-evaluation of the bromate PHG. Based on the currently available literature on the chemical, OEHHA concludes that the proposed PHG for bromate is appropriate.

Comment 16: "There should be no compulsion to produce a bromate PHG in the near term with the interpretive problems in the current draft, and flaws in the traditional approach, while significant new data that will affect the risk quantitation and credibility of the assessment are becoming available, and more is being developed. Bromate has been under regulatory control for many years, so there is no societal benefit to be achieved in the short run by publishing a PHG that is flawed. It is important to get the PHG right the first time, because the wrong conclusion will be costly and slow to be

corrected until the regulation is revised. Indeed, if you defer a decision at this time, OEHHA will have the first opportunity among the risk assessing and regulatory organizations to produce a revised risk assessment with a much stronger scientific support basis. Thus, we reiterate our request that you delay issuance of a bromate PHG pending receipt and examination of the latest developing detoxification information and the Physiologically Based Pharmacokinetic Model, and the revised risk assessment being generated."

Response 16: It should be noted that PHGs are not regulations, and confer no statutory obligation on any entity, public or private, to attain the stated goals. OEHHA's responses on risk assessment approach and use of data in the bromate PHG are addressed above in detail. Based on all the available data in the literature, OEHHA concludes that the bromate PHG calculation is appropriate. In our next evaluation, OEHHA will consider all new data available at that time.

Comments from Joseph A. Cotruvo, Joseph Cotruvo & Associates (May 27, 2009)

Comment 1: *The commenter provides preliminary data on toxicokinetics of bromate in rats and proposes future work on a PBPK model for rat and human.*

Response 1: OEHHA is happy to learn of the ongoing progress in bromate research. However, the data submitted is preliminary and unpublished. OEHHA will incorporate the pertinent results during the next evaluation of bromate PHG, after these data are published in a peer-reviewed journal.

Comment 2: "Given our preliminary data, we believe that standard risk assessment methodologies using the default linear DR assumptions utilized by USEPA, WHO and OEHHA, significantly overestimate the risk at levels found in drinking water."

Response 2: In the absence of chemical-specific information on distribution and metabolism of bromate at target sites, default assumptions are applied to provide a consistent approach in risk assessment. OEHHA agrees that risk calculated from default assumptions may be overestimated. These health-protective assumptions are applied to ensure the protection of public health, when specific data are not available.

Comment 3: "We recommend that the prudent course of action for OEHHA at this time would be to defer a decision on the PHG so that this new and developing information can be disseminated and reviewed."

Response 3: Based on all available data in the literature, OEHHA concludes that the animal data from DeAngelo *et al.* (1998) are adequate for development of the PHG. Although uncertainty is present in the assumption of linearity of the dose-response curve at low doses, application of the default assumptions are well justified from the available *in vivo* and *in vitro* mechanistic data and the multi-site tumor data. OEHHA expects that a validated physiologically-based pharmacokinetic model for humans will greatly benefit

the future risk assessment of bromate. A delay in finalization of the current PHG is not warranted, as PHGs are produced as expeditiously as possible, under the mandate of the California Safe Drinking Water Act, Health and Safety Code Section 116365 et seq.

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