Responses to Major Comments on Technical Support Document

Public Health Goal

For

Methyl Tertiary Butyl Ether (MTBE)

In Drinking Water

Prepared by

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INTRODUCTION

The following are responses to selected comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for methyl tertiary butyl ether (MTBE) as discussed at the MTBE workshop held on May 15, 1998, or as revised following the workshop. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they directly quoted from the submission; paraphrased comments are in italics.

The responses are arranged in two chronological divisions that generally correspond to the two drafts of the document. The first division includes comments received before, during, or shortly after the MTBE workshop held on May 15, 1998 when the first public draft was discussed. The second division includes the comments that came in at the end of the official 30-day comment period that ended on July 13, 1998. These comments concerned the revised document that included changes reflecting the workshop and earlier comments. Some commenters provided comments during both periods, which accounts for comments by the same entities appearing in both divisions.

These comments and responses are provided in the spirit of the open dialogue among scientists that was 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 AT OR AROUND THE MAY 15 MTBE WORKSHOP

Western States Petroleum Association (WSPA) (5/15/98)

Comment 1: "A two week period [between the document release on 4/30/98 and the workshop on 5/15/98] is not adequate unless OEHHA intends to reopen the entire document for further review and comment."

Response 1: The timing of the PHG review process is dictated by Health and Safety Code Section 57004 (a), which specifies a public workshop and a minimum 30-day comment period for the revised health evaluation. OEHHA made extra efforts to make the draft PHG document available for two weeks before the workshop. Comments could also have been submitted between the workshop and the release of the revised draft in early June 1998. During the official 30-day comment period, which ended in July 1998, the entire document was open for additional revisions as needed. In the case of MTBE where the Department of Health Services (DHS) has a statutory deadline of July 1, 1999 for establishing a primary MCL, based in part on OEHHA's PHG, there was less flexibility for extending the comment period.

Comment 2: "The Belpoggi et. al. gavage studies that drive OEHHA's draft PHG are considered by the National Research Council and the USEPA to be sufficiently flawed to preclude their use in characterizing the cancer potential of MTBE in humans."

Response 2: The comment that the Belpoggi et al. study drives OEHHA's PHG is inaccurate. Numerically, the values from Belpoggi et al. that figure in OEHHA's mean carcinogen slope factor (CSF) estimate are lower on average than that derived from the Chun et al. inhalation study: i.e., 1.7E-3 $(mg/kg\text{-}day)^{-1}$ with Belpoggi et al., and 1.8E-3 $(mg/kg\text{-}day)^{-1}$ for the Chun et al. data only. OEHHA scientists believe that a more robust CSF estimate is achieved by including the Belpoggi et al. data even though it results in a slightly lower potency. The statement about the Belpoggi study being "sufficiently flawed to preclude" its use is misleading. Actually, U.S. EPA (1997) noted limitations in the study and quoted from the National Science and Technology Council (NSTC) 1997 report. Also, it used the Belpoggi et al. study data in calculating margin of exposures (MOEs) for human cancer risks giving MOEs of 20,000 to 40,000 for drinking water concentrations of 40 to 20 μg/L respectively (see Table 1, U.S. EPA, 1997). OEHHA considers the results of the Belpoggi et al (1995, 1997, 1998) oral study in rats, the Chun et al (1992) and Bird et al. (1997) inhalation study in rats, and the Burleigh-Flayer et al. (1992) inhalation study in mice, sufficient to conclude that MTBE is carcinogenic in animals and potentially carcinogenic in humans chronically exposed to MTBE.

Association of California Water Agencies (ACWA) (5/12/98)

Comment: *It is likely that a number of public water systems will, if given adequate time to analyze the technical documentation, want to provide comments. For that reason we request that the public comment period be extended for 30 days.* (Paraphrased)

Response: The timing of the PHG review process is dictated by Health and Safety Code Section 57004 (a), which specifies a public workshop and a minimum 30-day comment period for the revised health evaluation. OEHHA made extra efforts to make the draft PHG document available for two weeks before the workshop. Comments could also have been submitted between the workshop and the release of the revised draft in early June 1998. During the official 30-day comment period, which ended in July 1998, the entire document was open for additional revisions as needed. In the case of MTBE where the DHS has a statutory deadline of July 1, 1999 for establishing a primary MCL, based in part on OEHHA's PHG, there was less flexibility for extending the comment period.

County Sanitation Districts of Los Angeles County (5/15/98, 6/19/98)

Comment 1: Use of U.S. EPA's proposed guidelines for carcinogen risk assessment: *OEHHA should use other methods.* (Paraphrased)

Response 1: OEHHA used both the linearized multistage model (LMS) approach for comparison as well as the LED methodology proposed by U.S.EPA in their 1996 guidelines. In our recent experience the LED methodology gives potency values that are usually about 5% to 10% *lower* (less potent) than the LMS methods. In the case of MTBE, the results of the two methods were nearly identical. It is uncertain what other methods the commenter would like OEHHA to use.

Comment 2: Daily water intake: *use lower values*. (Paraphrased)

Response 2: The default value for water ingestion is the same as used by U.S. EPA, Office of Water, and is also documented in OEHHA's draft technical support document "Exposure Assessment and Stochastic Analysis" published in December, 1996. This value represents approximately the 90% upper confidence level on tap water consumption and the average total water consumption.

Comment 3: *Do not use 50% inhalation absorption for MTBE but rather a lower number.* (Paraphrased)

Response 3: Nihlen et al. (1998a) cited in our PHG draft observed a respiratory uptake of 42%-49% in human subjects exposed to MTBE for two hours at 5, 25, and 50 ppm. Fifty percent is a typical default but in this case it is especially supported by actual data on MTBE uptake in humans.

Comment 4: *The Henry's law constant is too high; use a lower value to give an inhalation intake from showering, etc., of 2.3 Leq/day instead of 3 Leq/day.* (Paraphrased)

Response 4: Our analysis included a range of values for Henry's law constant, which varies with temperature, and various levels of water intake. Assuming 50% inhalation absorption (see Response 3 above), the total MTBE intakes (from all exposure routes) ranged from 2.5 to 4.0 Leq/day. Our choice of 3 Leq/day is approximately in the middle of the range of values calculated.

Comment 5: *Do not use 1E-6 but rather 1E-5 as the acceptable lifetime extra cancer risk criterion.* (Paraphrased)

Response 5: For criteria applied to environmental media, such as air and water, OEHHA has used the 1E-6 criterion for extra lifetime cancer risk. The 1E-5 cancer risk criterion is specifically associated with Proposition 65 only (i.e., risk-specific intake levels) and is defined as a level of significant risk. According to the California law defining PHGs, OEHHA must set these at levels with no significant health risk. For cancer, the negligible risk criterion currently used by U.S. EPA and OEHHA is 1E-6. In developing the MCL for MTBE, DHS will take technical and economic factors as well as the PHG into consideration. U.S. EPA usually sets a maximum contaminant level goal (MCLG) value of zero for carcinogens. The PHG is generally comparable to the MCLG and not the MCL.

Comment 6: *Does MTBE cause cancer in humans?* (Paraphrased)

Response 6: Direct information on whether MTBE causes cancer in humans is not available. Environmental regulation does not require evidence of cancer causation in humans before prudent steps are taken to limit exposures to agents that are potentially carcinogenic in humans. Many carcinogens are regulated without convincing epidemiological support solely on the basis of animal data and the belief that, in general, chemicals that cause cancer in relatively few animals at high doses may also do the same in much larger numbers of people at lower doses.

Oxygenated Fuels Association, Inc. (OFA) (5/15/98)

Comment 1: "MTBE is not genotoxic in numerous assays, and, therefore, is not likely to be a genotoxic carcinogen. Therefore, the use of linear extrapolation to estimate cancer potency is not justified."

Response 1: We accept that MTBE is probably not genotoxic as indicated in the various assays conducted to date. However lack of genotoxicity does not establish the mode of carcinogenic action. Because there is no clear mode of action indicated for the carcinogenic action of MTBE observed in the three animal studies evaluated, OEHHA has used a default approach of linear extrapolation as recommended in U.S. EPA's 1996 proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, Federal Register, Vol. 61, No. 79, Tuesday, April 23,1996, 17960-18011). This is explained at some length in the technical support document and was also covered at length at the MTBE workshop held in Berkeley on 5/15/98.

Comment 2: *MTBE is not a promoter therefore the use of linear extrapolation is not justified.* (Paraphrased)

Response 2: In the one promotion study published to date, MTBE appears to lack the ability to promote liver tumors initiated by N-nitrosodiethylamine in mice. OEHHA decided not to include the mouse liver endpoint in its CSF estimate. Also, see response to Comment 1 on lack of data supporting a mode of carcinogenic action.

Comment 3: *MTBE at high doses has produced tumors in laboratory animals as a result of processes that are not applicable to humans exposed to low doses of MTBE. Therefore the most appropriate approach is the margin of exposure (MOE).* (Paraphrased)

Response 3: The mechanisms by which MTBE increases the incidence of tumors in animals and could potentially be carcinogenic in humans has not yet been established. Ongoing research projects may produce useful insights, but at present OEHHA scientists are not convinced that the proposed processes are clearly evident. The MOE approach to assessing carcinogenic risks of MTBE exposure to human populations was conducted by U.S. EPA (1997) and resulted in MOE values ranging from 40,000 to 550,000 for a 20 μg/L MTBE drinking water concentration. We believe these figures are in reasonable agreement with OEHHA's 1E-6 extra lifetime cancer risk value of 13 μg/L.

Comment 4: *Male rat kidney tumors are likely to result from secondary, non-genotoxic tissue damage caused by otherwise highly toxic doses of MTBE unlikely to be experienced by humans.* (Paraphrased)

Response 4: OFA has proposed that kidney tumors in rats exposed to MTBE occur only following deposition of α_{2u}-globulin in the kidney cells. This proposed mode of action for MTBE induced kidney tumors has been argued at great length and there is some difference of opinion among scientific experts on this point. OEHHA scientists have reviewed all the information available on this question and found that the available data on renal tumorigenesis indicate that MTBE induces only mild accumulation of the α_{2u}-globulin protein and only mild or partial expression of α_{2u}-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non-α_{2u}-globulin rat nephropathy in both male and females (NSTC 1997). Thus, based on the available evidence, only one of the three criteria established by U.S. EPA (1991) for causation of an α_{2u}-globulin effect has been met in the case of MTBE induced renal carcinogenesis in male rats. Since only one of the criteria has been met it does not appear that the scientific evidence supports a conclusion that the male rat kidney tumors are likely to result from secondary non-genotoxic tissue damage. The commenter did not mention the U.S. EPA criteria for evaluating mechanistic data with respect to male rat kidney tumors.

Comment 5: *Female mouse liver tumors are the result of high, non-genotoxic doses of MTBE interfering with the tumor suppressor mechanisms of estrogen in the female mouse liver that are unlikely to be present in the human liver.* (Paraphrased)

Response 5: While this is an interesting concept, the evidence provided by OFA is insufficient in our view to support it. The studies cited, e.g., Casanova & Heck (1997) on DNA-protein cross-links and RNA-formaldehyde adducts arising from MTBE metabolism, suggest that the formaldehyde metabolite of MTBE is probably not involved in the induction of liver cancer in mice. These data and others cited still do not indicate what is involved in the carcinogenic mode of action. Also it might be useful to note that hepatocellular carcinomas were found at the high dose in male mice. Due to the lack of specific evidence, OEHHA has assumed the parent compound, MTBE, is the cause.

Comment 6: "The evidence suggests strongly that the testicular tumors in rats were likely to result from factors other than MTBE."

Response 6: The studies cited by OFA are not sufficient for OEHHA to discount these tumors as being of potential relevance to human health effects resulting from continued exposure to low levels of MTBE. Testicular tumors were noted in two separate studies, in two strains of rats, by two routes of administration. The commenter discounts the testicular tumors observed in the Bird et al. (1997) study as well as a clearer dose response seen in the Belpoggi et al. (1998) study. While the relevance of almost any animal tumor to humans can be debated with respect to the probability of strict concordance of sites between species, which is generally low, the observation of this tumor in both the Belpoggi et al. and Chun et al. studies adds weight to the finding and supports the veracity of both studies. OFA has argued that all of the observed tumors while not artifacts are irrelevant to human cancer risk assessment based on interesting but incomplete evidence. OEHHA concluded that it is unlikely that all of these tumors can be irrelevant particularly when a plausible mode of action for any one of them is considered lacking.

Jonathan Borak & Company, Inc. (5/15/98)

Comment 1: "There is nothing 'wrong' with these techniques and manipulations. They are often necessary and useful. But their use leads to unavoidable uncertainty. The problem with the OEHHA document is its failure to acknowledge the large uncertainty which underlies its conclusions. Instead, it presents that conclusion as a precise point estimate (precisely "14 ppb"), implying that its risk assessors can aim and shoot with the certain accuracy of world class marksmen."

Response 1: It could be argued if uncertainty is introduced by the risk assessment or really preexists and is only approximately revealed by the assumptions employed in a specific assessment. Terms such as accuracy and precision are seldom used in risk assessment because of the many uncertainties that are unavoidable. The number 14 does not connote any special degree of accuracy or high certainty. The calculated number was 13.72 ppb. (The PHG value has now been revised and is now 13 ppb.) We use either one or two significant figures in expressing the final PHG. For MTBE, if one significant figure was used, the PHG would be 10 ppb. In the draft document, we presented the PHG as two significant figures because we could scientifically justify the use of two. The uncertainties of our analysis are more completely detailed in the revised Risk Characterization section in terms of ranges of quantitative estimates based on varying assumptions. To further address these concerns, additional information has been added to the document summary including a range of cancer risk and an estimate based on an uncertainty factor approach.

Comment 2: "I can point to some key places where substantial uncertainty entered their risk analysis: The decision to ignore the role of alpha-2u-globulin nephropathy in MTBE-associated kidney tumors."

Response 2: OEHHA scientists did not ignore the proposed α_{2u}-globulin mechanism but were unconvinced that the actual findings in the MTBE-treated animals justified assuming that this proposed mechanism was at work in the causation of rat kidney tumors. For example it has proposed that kidney tumors in rats exposed to MTBE occur only following deposition of α_{2u}-globulin in the kidney cells. This proposed mode of action for MTBE induced kidney tumors has been argued at great length and there is some difference of opinion among scientific experts on this point. OEHHA scientists have reviewed all the information available on this question and found that the available data on renal tumorigenesis indicate that MTBE induces only mild accumulation of the α_{2u}-globulin protein and only mild or partial expression of α_{2u}-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non-α_{2u}-globulin rat nephropathy in both male and females (NSTC 1997). Thus, based on the available evidence, only one of the three criteria established by U.S. EPA (1991) for causation of an α_{2u}-globulin effect has been met in the case of MTBE induced renal carcinogenesis in male rats. Since only one of the criteria has been met it does not appear that the scientific evidence supports a conclusion that the male rat kidney tumors are likely to result from secondary non-genotoxic tissue damage. The uncertainty is not added by the risk analysis but exists because the role of α2u-globulin in MTBE induced rat kidney carcinogenicity has not been established.

Comment 3: "The decision to aggregate lymphomas and leukemias, thereby achieving statistical significance not otherwise present."

Response 3: OEHHA did not aggregate the data since this is the form in which they were reported by Belpoggi et al. OEHHA scientists believe that the aggregation is acceptable for the strain of rat used.

Comment 4: "The decision to ignore possible non-genotoxic mechanisms for testicular and other tumors"

Response 4: As noted elsewhere, these "possible non-genotoxic mechanisms" do not yet constitute plausible modes of carcinogenic action with reasonable supporting evidence. If the evidence supporting it were available it would be reviewed and considered.

Comment 5: "The decision to treat MTBE, rather than its metabolites, as the cause of effects in animals 'due to lack of a clear mode of action of TBA or other MTBE metabolites."

Response 5: This does introduce uncertainty as noted, and our assessment would have been more difficult if the TBA metabolite were assumed to be the carcinogenic agent. For example the physiologically based pharmacokinetic (PBPK) model used to estimate internal doses did not perform well in predicting TBA kinetics. On the other hand, the available data justify focusing on MTBE as the carcinogen until new data show otherwise.

Comment 6: "The decision to employ an imprecise PBPK model to estimate tissue doses and the decision to rely upon an Area-Under-the-Curve dose measure despite OEHHA's "uncertainty whether other dose metrics would be superior.'"

Response 6: Actually, the PBPK model analyses are quite precise in the sense that repetitive simulations give the same results within a few tenths of one percent. OEHHA thinks the commenter is referring to the accuracy of the dose metrics in terms of providing a better fit of the dose-response data. That is, is the dose metric more closely related to the effect than the applied dose or some alternate metric? The blood AUC metric is typically employed in cancer risk assessment where continuous low level exposure of target tissues is thought more related to cancer effects that transient peak concentrations, another possible metric. Although the MTBE blood AUC metric was superior in fit to the data compared to the applied dose, the difference was not large. As the commentator noted, we did acknowledge this uncertainty.

ARCO (5/15/98)

Comment 1: *The use of animal tumor data and linear dose response approach, is it justified?* (Paraphrased)

Response 1: As noted elsewhere in these responses, OEHHA interprets the proposed 1996 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) as recommending a default linear approach where evidence supporting a non-linear (MOE) approach is lacking. OEHHA scientists are currently not convinced that the evidence clearly supports a non-linear approach or the use of both approaches, as would be indicated by equivocal data supporting linear and non-linear approaches.

Comment 2: *You have developed both cancer-based and non-cancer numbers, but the latter is buried in the document. You should move it up front and mention in the summary along with the cancer based number.* (Paraphrased)

Response 2: OEHHA has accommodated the comment and mentioned the non-cancer number in the summary section of the document.

Comment 3: *The weight of evidence statement should be revised. For example, you have a statement in the summary that the level of evidence of carcinogenicity exceeds the level of evidence for most other regulated carcinogens. I think the risk managers are going to perceive that as a weight of evidence statement.* (Paraphrased)

Response 3: This statement has been removed from the revised summary although it is one weight of evidence factor considered by OEHHA scientists and we still believe it to be reasonably accurate.

Comment 4: *You mentioned conclusions of NSTC but neglected to put in the many cautions that they put in when they calculated or used extrapolation models and how cautious one should be in using those for regulatory decision making.* (Paraphrased)

Response 4: The National Science and Technology Council (NSTC) raised concerns which could not be resolved in the time frame of our PHG development schedule. We interpret NSTC cautions as dependent upon the regulatory mandate of those using the study data. The PHG mandate and the specific legal language leave little doubt that in the case of ambiguity, OEHHA

is to use the most health-protective assumptions in developing and adopting PHGs. U.S. EPA is both risk assessor and risk manager, and it operates under a different mandate which requires it to consider economic factors. The use of the MOE approach suits U.S. EPA's overall mandate. OEHHA is mandated to consider only public health factors for PHGs whereas economic factors and other non-public health factors may be taken into account by DHS in setting the MCL.

Communities for a Better Environment (5/15/98)

Comment 1: "My major concern today about MTBE is that it pits economics against health. It's an environmental justice issue. I'm deeply concerned. MTBE needs to be banned entirely. There is no need for MTBE. The air would be clean with reformulated fuel alone and technology that's used by Detroit with catalytic converters."

Response 1: OEHHA has no authority to ban MTBE but rather to determine safe levels of human exposure via drinking water. That is what OEHHA has done in adopting this PHG for MTBE.

Comment 2: "As we sit here and discuss this problem today, MTBE has been in the news all across the world. I just got a call from Russia. I was up in Vancouver where they're trying to introduce it up there in newly formulated fuels. This is devastating. Again, it pits economics against human justice. It should be banned. Set the level, the PHG at zero. Let's get rid of MTBE. We don't need it."

Response 2: The law does allow OEHHA to set a PHG at zero in order to meet the mandate of the law. OEHHA has interpreted this mainly with respect to meeting the timing mandates (i.e., 25 PHGs per year) and not that any particular PHGs would routinely be set at zero. In the PHGs OEHHA has adopted to date it has followed the definition of the PHG provided in the statute and given in the preliminary pages of each PHG technical support document including that for MTBE. As noted elsewhere, U.S. EPA has a policy of setting MCLG values at zero for carcinogens with an alphanumeric classification of B or above. OEHHA scientists believe that such zero standards have little scientific meaning or justification and may only find temporary use for administrative reasons.

City of Santa Monica (5/15/98)

Comment 1: "We do have some concerns. It probably doesn't concern this panel, but the way the Public Health Goals are being established. We've got some concerns that our public is going to hear very shortly this number of 14 ppb and they're not going to understand what it is."

Response 1: We acknowledge that there is a communication issue with the adoption of so many PHGs over a relatively short period. PHGs are not entirely new to the state's drinking water law and were referred to as recommended public health goals (RPHGs) in the amended version of the California Safe Drinking Water Act of 1989 (Sher, AB 21). OEHHA has prepared guidance for public water systems affected by the reporting requirements of the 1996 law. In addition, OEHHA is preparing an information document on PHGs for the public.

Comment 2: "The Public Health Goals--the message that we're sending as far as what a Public Health Goal is as opposed to a standard that's enforceable, and MCL, primary standard, secondary standard, it's very confusing to the public."

Response 2: OEHHA appreciates the complexity of the public communication issues. However state drinking law operates under the authority of the federal Safe Drinking Water Act and its terminology is quite similar. Secondary standards for esthetic quality, like taste and odor, are advisory at the federal level as are the health based goals (MCLGs), but the federal MCL or primary standard cannot be exceeded. In California, secondary standards are generally complied with since the objective is to supply not only safe but also pure water. PHGs cannot be enforced but there is a reporting requirement for some systems. PHGs are set at a level of insignificant risk. MCLs are established at a level to balance risk with other important factors. State MCLs are enforced.

Comment 3: "We're not going to comment on whether 14 is a good number or a bad number or whatever number it is. We're looking at good science to develop that number, and we're hoping this process will develop that number."

Response 3: OEHHA believes all the relevant issues and uncertainties have been raised with respect to assessing human risks of exposure to MTBE in drinking water. However, we have to acknowledge gaps in our understanding of the mode of action of MTBE in the animal studies exhibiting increased cancer incidence. The law requires OEHHA to adopt a PHG value based on the current database which in this case is incomplete. This is not an unusual situation in cancer risk assessment. The law also requires periodic updating and revision of PHGs to accommodate new scientific information.

RESPONSES TO MAJOR COMMENTS RECEIVED AT THE CLOSE OF THE PUBLIC COMMENT PERIOD

California-Nevada (Cal-Nev) Section, American Water Works Association (AWWA) (7/13/98)

Comment 1: "OEHHA has used a much higher water consumption rate (3 liters/day) than both USEPA or OEHHA. OEHHA itself has always used before (2 liters/day) in doing risk assessments for numerous volatile chemicals where both inhalation and ingestion could be involved."

Response 1: The commenter is incorrect in the statement that OEHHA has always used 2 L/day to assess exposure to volatile organic chemicals (VOCs) via drinking water. Since 1988, OEHHA has employed the concept of multi-route exposure to VOCs in numerous risk assessments, many of which are the bases of current state MCLs. Total exposure from drinking water is usually expressed as the sum of ingestion, inhalation and dermal exposures resulting from typical household uses of tap water, in liter equivalents/day (Leq/day). Values for typical VOCs are around 6 to 7 Leq/day but may range as high as 30 Leq/day for highly volatile

chemicals. U.S. EPA has studied this issue for many years, but as yet has not issued detailed guidance. U.S. EPA did, however suggest a default value of 2 Leq/day for inhalation exposure to VOCs during showering only (U.S. EPA, Guidance on estimating exposure to VOCs during showering, Risk Assessment Forum, Washington, DC, 7/10/91). The value proposed by OEHHA of 1 Leq/day for all noningestion routes or 3 Leq/day total is near the lower end of the VOC multi-route exposure range. The rationale for this approach has been explained in numerous risk assessments and in the published literature. (See also response 4 to Los Angeles County comments above.)

Comment 2: "OEHHA continues to state that adopting a PHG has no regulatory impact and OEHHA does not follow the normal required public notice and hearing process. Cal-Nev AWWA does not understand OEHHA's failure to follow the correct procedures."

Response 2: The statute requiring adoption of PHGs for all existing state MCLs and MTBE specifically provides that the PHGs are not enforceable. They are to be taken into account by DHS in setting the MCL, which is enforceable. As the PHG for MTBE or any other substance is not enforceable it is not a regulation. Since adoption of a PHG is not a regulation, it is not subject to the public notice or hearing process of the Administrative Procedure Act (APA) or any other provision of that law. In developing an MCL for MTBE, DHS is required to follow the "correct procedures" of the APA.

Jonathan Borak, MD (7/9/98)

Comment: "I was gratified that your second draft made efforts to address those concerns and to adopt my recommendations. Nevertheless, those efforts seem insufficient to avoid important misunderstanding….I remain convinced that all but the most knowledgeable scientists will be unable to understand the contents of your draft, the inherent limits and uncertainty of your analysis, and the scientific basis of your conclusions….For example, the following discussion of uncertainty with respect to the calculated cancer slope factor has been added to the text in three places…Following is a translation of those techno-jargon statements into plain English: Our calculation of the cancer potency of MTBE in humans is based on data from studies of rats and mice because there are no relevant human data. The mathematical and scientific methods that we used are generally accepted for this purpose, but their use causes our conclusions to be uncertain. It is possible that we have underestimated its cancer potency of MTBE in humans, but that seems unlikely. On the other hand, we may have over estimated its cancer potency in humans; in fact, it is plausible that MTBE does not cause human cancer."

Response: We acknowledge that the PHG support document is written by scientists to be defensible in the scientific community. Therefore, some use of scientific terms is unavoidable in a complex risk assessment document. The particular statements addressed by the commentator were composed after a considerable discussion and are scientifically accurate. The alternate plain English proposal, while easy to read, is not precise. For example the cancer slope factor was based on an average of the rat tumor sites and does include the mouse-based value. Also, the statement that the uncertainty is a result of applying our mathematical and scientific methods is not entirely true. The lack of knowledge about key processes induced by MTBE is a major cause of uncertainty. That is, the uncertainty is due to data gaps in our scientific knowledge not

a result of our scientific procedures. Public communication concerns and activities underway to address them are discussed in response to earlier comments.

State of New Jersey, Department of Environmental Protection, Bureau of Transportation Control and Division of Science and Research (7/15/98)

Comment 1: "When discussing the public health goals (PHGs) for MTBE, the above-referenced document states in three places that, 'It is plausible that the true value of the human cancer potency has a lower bound of zero based on statistical and biological uncertainties.' The public may interpret this to mean that the margin of safety for MTBE in drinking water *should be* set at zero (0) ppb rather than 14 ppb due to lack of data on humans. -Since this is completely contrary, I recommend that Cal-EPA clarify or revise these statements to avoid misunderstandings."

Response 1: The statement addressed by the commenter is complex but correct. OEHHA is referring to the plausible bounds on the slope of the low dose response relation. A value of zero would indicate a response threshold. While the law does allow OEHHA to adopt a zero value for the PHG, we do not believe that the concept of zero slope in units of $(dose)^{-1}$ and zero PHG in units of mass per volume concentration (ppb) are easily confused. A less technical separate brochure explaining PHGs and supporting methodology in terms more understandable to the general public is in preparation.

Comment 2: "When discussing the cancer slope factor (CSF), the above referenced document states, 'While it is theoretically possible that the true human CSF could exceed this value, that is considered unlikely.' -The public may interpret this statement to mean that the human CSF will exceed this value and that 14 ppb is not protective enough of public health, yet because Cal-EPA considers this to be an 'unlikely event', the PHG was set to 14 ppb."

Response 2: Such an interpretation is inevitable in all conclusions based on statistical analysis. The CSF is based on the 95% lower bound on the dose causing a 10% tumor incidence (LED_{10}) and an assumption about interspecies extrapolation from rodents to humans. To the extent that these methods overestimate the true human $LED_{10,}$ the true human CSF will be underestimated. Since there are no relevant human cancer data to compare with animal-based CSF estimates, we can only assume based on past experience with such procedures that an underestimate of the human CSF and resulting theoretical risk at low dose is unlikely. See response to previous comment.

Comment 3: "Many of the documents focus primarily on the disadvantages of adding MTBE to gasoline with very little discussion (if any) about the benefits of oxygenates, thus promoting regressive alternatives (e.g., going back to 'traditional' gasoline with higher levels of benzene and other known human carcinogens - a request which is often made by the public who oppose the use of MTBE)."

Response 3: Assessing the benefits of MTBE as a fuel oxygenate is beyond the scope of OEHHA and its PHG technical support document. However, this topic has been addressed in a University of California report (Health and Environmental Assessment of MTBE, Report to the

Governor and Legislature of the State of California as Sponsored by SB 521, http://tsrtp.ucdavis.edu/mtberpt).

Comment 4: "The Public Health Goals derived by California for MTBE based on non-carcinogenic effects (47 μg/L) and carcinogenic effects (14 μg/L) differ by a factor of three. This can be regarded as close agreement when all of the assumptions and uncertainties which enter into the derivation of these values are considered."

Response 4: Agreed. The values bracket the public health advisory and consumer acceptability range of 20-40 μg/L established by U.S. EPA in 1997.

Western States Petroleum Association (WSPA) (7/13/98)

Comment 1: "We continue to disagree with the approach taken by OEHHA to treat MTBE as a non-threshold carcinogen and using the linearized multistage model to derive a PHG. The mutagenicity and mechanistic data available for MTBE do not support this approach." *The report also gives an alternative health protective value of 47 ppb which includes an uncertainty factor for potential carcinogenicity. This value would be more appropriate for the PHG.* (Paraphrased)

Response 1: The PHG value of 13 ppb is based on a low-dose linear extrapolation from the LED_{10} and not on the linearized multistage model (LMS). Estimates based on the LMS are included in the document for comparative purposes and because experience with the LED_{10} approach is comparatively limited. The software previously used for the LMS extrapolation is now used only to fit the polynomial dose equation to the data in the observed range and to calculate the ED_{10} and LED_{10} values. Extrapolation is essentially model free, i.e., the carcinogen slope factor or CSF = $0.1/LED_{10}$. OEHHA interprets the California Safe Drinking Water Act of 1996 as requiring the choice of the more health protective value of 13 ppb, which is based on cancer, rather than the 47 ppb value based on kidney weight effects for the PHG. Additionally, OEHHA scientists conclude that the data on the carcinogenicity, metabolism, and pharmacokinetics of MTBE are sufficient to require a quantitative assessment of cancer risk due to exposure via drinking water.

Comment 2: "Furthermore it appears that including a 3 liter equivalent exposure in addition to a 20% Relative Source Contribution factor is an overly conservative approach in dealing with non-drinking water exposures to MTBE. It is also not consistent with the approach used by EPA in previous Health Advisories for MTBE."

Response 2: OEHHA and U.S. EPA methodology on relative source contribution (RSC) and multi-route exposures to VOCs (i.e., relative route contribution to the source drinking water) are not the same. OEHHA has always considered sources and routes separately whereas U.S. EPA does not use multi-route exposure estimates for VOCs. Based on the high water solubility of MTBE, OEHHA has used a lower value for inhalation exposure than for other VOCs. The value we chose for the RSC was the default of 20% or 0.2. It is true that a 20% RSC is the more conservative default, and we have used 40% and 80% for other chemicals based on their likely occurrence in other sources such as ambient air and food. However, considering that the MTBE environmental occurrence data are still developing in the State (in air and in water) we conclude

that the 20% default is justified at the present time because there are apparently significant non water exposures that are not yet fully characterized. For example the ambient air MTBE concentration statewide is 2 ppb and in the Los Angeles air basin it is about 4 ppb. These values represent 3 to 6 $x10^{7}$ lifetime extra theoretical cancer risks for the exposed populations. Since there are other airborne exposures in addition to ambient air associated with vehicle fueling, commuting, etc., we believe that additional California MTBE exposure data need to be developed in order to depart from the 20% default.

U.S. Environmental Protection Agency, Office of Water (6-24-98)

Comment: "Cal/EPA has derived a PHG of 14 ppb based on the carcinogenic effects observed in experimental animals (Belpoggi et al., 1995,1997). As you are aware, the U.S. EPA did not elect to quantitate the data from the Belpoggi et al. study (1995), since it had not been audited as recommended by the NRC panel report. There is, at the present time, little possibility that the U.S. EPA's position will change in the foreseeable future. This is not meant as a criticism of your decision to use the Belpoggi data et al. reports (1995, 1997), but rather a statement that our two agencies have viewed the MTBE data differently and one that, I am sure, will be raised by many commentators."

Response: The PHG of 13 ppb is based on carcinogenic effects observed in rats in two independent series of bioassays: an inhalation study by Chun et al. (1992) and a gavage study by Belpoggi et al. (1995, 1997, 1998). It is true that we viewed the data differently from U.S. EPA in that we calculated LED_{10} values for each of the four tumor sites, calculated CSF's ($0.1/LED_{10}$) for each and averaged the three most quantitatively similar sites while U.S. EPA calculated LED_{10} values for three tumor sites (including one from Belpoggi et al.) and provided margins of exposure for the 20-40 μg/L acceptability range. We view our mandate under the California Safe Drinking Water Act of 1996 to be adoption of a single value PHG that is associated with no significant adverse health effects over a lifetime of exposure. We also interpret the proposed 1996 U.S. EPA guidelines for carcinogen risk assessment as requiring a linear low dose approach when there are insufficient data with respect to the mode of action of the carcinogenic agent. OEHHA scientists conclude that there are presently insufficient data to establish a convincing mode of action for any of the four tumor sites observed in the two rodent species tested. Accordingly, OEHHA used the methodology it did to meet its mandate of adopting a single value PHG that is associated with no significant adverse health effects over a lifetime of exposure.

U.S. Environmental Protection Agency, Office of Water (7-13-98)

Comment 1: "The document seems to be a 'patchwork' in nature…..This draft needs careful editing and synthesis to become a 'readable' document."

Response 1: The draft document was assembled by six OEHHA scientists over a relatively brief period of approximately five months and therefore some unevenness in the "readability" is unavoidable. Given the short timeline of the statutory mandate of the Local Drinking Water Protection Act of 1997 which provided OEHHA with less than one year to adopt a PHG for MTBE, we do not have more time to edit the document. OEHHA's MTBE assessment depends

to varying degrees on the work of other agencies including U.S. EPA to meet the timing demands of the law. We believe that the current draft of the technical support document is sufficiently "readable" to fulfill its purpose in supporting the adoption of a PHG for MTBE. OEHHA has also benefited from external peer review by the University of California system and by the mandated SB 1082 public workshop on MTBE.

Comment 2: "EPA has never derived a RfD for MTBE, so this should be corrected."

Response 2: The reference to the RfD has been corrected.

Senator Richard L. Mountjoy, California State Senate (7/13/98)

Comment 1: "It is my belief that 14 ppb in drinking water is much too high to assure the safety of Californians. The level should be set between 2.5 ppb and 5 ppb at a maximum though personally I believe *any* level of MTBE in our water represents a risk to human health."

Response 1: OEHHA acknowledges your concern about the potential health effects of MTBE exposure. OEHHA has conducted a comprehensive risk assessment of MTBE within a very limited time frame to meet a statutory mandate in adopting a PHG. The PHG we have developed is supported by the available science although there is some unavoidable uncertainty due to lack of key information and the use of statistical methodology. Our approach is to use health-protective assumptions when scientific data are lacking. For example, the OEHHA risk assessment of MTBE uses a linear low-dose extrapolation because of the lack of convincing evidence supporting a nonlinear mode of action. A consequence of this procedure is that a theoretical risk is calculated for *any* level of exposure. The key concept to appreciate is that of negligible risk. OEHHA presently considers individual lifetime risks at or below one per million (1×10^{-6}) as insignificant. This is similar to U.S. EPA practice for air and water contaminants. The OEHHA assessment identified 13 ppb as the drinking water concentration associated with negligible cancer risk. OEHHA could identify no other human health hazards associated with exposures at MTBE concentrations (or equivalent doses) below this level. However, if more extreme, worst case, assumptions are employed , the negligible risk level could be reduced to 2.5 ppb as described in our technical support document. OEHHA generally has not based its proposals on the worst case assumptions but such possibilities are included in the Risk Characterization section of our technical support documents.

Comment 2: "It is important that OEHHA evaluate whether the synergistic effect of MTBE with other gasoline components affects human health. Looking at MTBE alone is not enough to assure safety. People are being exposed to a chemical that may be reacting with other chemicals in the gasoline. That risk has not been adequately addressed in this report."

Response 2: OEHHA was requested by the DHS to develop a PHG for exposure to MTBE in drinking water rather than in gasoline. While many of the concerns expressed in this comment are potentially valid and worthy of research, they are necessarily beyond the scope of the current assessment. The issue of synergism is one that is of concern to us and the scientific community. However, there currently is no way to determine if MTBE is acting synergistically with other compounds in the environment. This is one of the reasons that we have developed health protective approaches when faced with data gaps. The University of California report addresses

some of the exposure issues mentioned in the comment (Health and Environmental Assessment of MTBE, Report to the Governor and Legislature of the State of California as Sponsored by SB 512, Volume II, Human Health Effects, November 12, 1998, http://tsrtp.ucdavis.edu/mtberpt)

Comment 3: "Individuals exhibit health symptoms when being exposed to MTBE while driving, sitting in cars, refueling or smelling gasoline with MTBE. The symptoms disappear when they were not exposed to MTBE-laced gasoline, but reappeared when they were re-exposed. Whether humans are exposed to MTBE alone, or to its combustion byproducts, or its interaction with one or more of the other components of gasoline needs to be analysed."

Response 3: These are valid comments although it has been difficult to establish an MTBE-based causality in controlled experiments. The University of California has established a research program mandated and funded by SB 521. Among the research projects discussed at a recent MTBE Research Workshop in Davis was a detailed evaluation of MTBE combustion byproducts in California reformulated gasoline. This work is being directed by Dr. Catherine Koshland of University of California, Berkeley and is detailed in the University of California report (Health and Environmental Assessment of MTBE, Report to the Governor and Legislature of the State of California as Sponsored by SB 521, November 12, 1998). Also it should be emphasized that OEHHA's PHG includes a relative source contribution which assumes the majority of exposure will occur via non-water sources, principally airborne MTBE.

Comment 4: "…some of the illnesses associated with MTBE are quite serious. MTBE causes a variety of cancers in animals, including leukemia, lymphoma, liver cancer, kidney cancer, and testicular cancer. As you know, when a substance causes cancer in animals, it may also cause cancer in humans. The North Carolina Department of Environment, Health and Natural Resources considers MTBE a probable carcinogen, an assessment with which I agree. Whether MTBE is labeled a possible carcinogen or a probable carcinogen, clearly MTBE in gasoline will trigger cancer in some of the people who are exposed. Until there are studies assuring MTBE does not cause human cancer, it is unconscionable to permit drinking water to contain appreciable amounts of this chemical."

Response 4: OEHHA acknowledges your concern about potential cancer risk from MTBE exposures. OEHHA does not have a classification system for ranking carcinogens, but our assessment of MTBE is similar to that mentioned for North Carolina. OEHHA evaluated both cancer and noncancer toxic endpoints and based its proposed PHG for MTBE on the cancer endpoint as evidenced in three animal bioassays. We believe our assessment is sufficiently health protective and in particular with respect to cancer risk, if we have erred at all, it is clearly on the side of public health protection.

Comment 5: "As we consider the impact of MTBE, we must consider how absolutely pervasive MTBE can be because of its high solubility. Recently in the State of Maine a single car overturned. Testing as of last week showed that MTBE had entered 16 private wells from that one incident, with 11 of the wells above 25 ppb." "In California, we are not even looking at water which may have been contaminated as the result of vehicle accidents. This certainly could have a widespread effect on California's water."

Response 5: As noted above, SB 521-funded research on MTBE by the University of California involves a number of projects. A comprehensive study of the state-wide distribution of MTBE in surface drinking water supplies is being directed by Dr. John E. Reuter, University of California, Davis. The project involves an integrated assessment of sources, fate and transport, ecological risk and control options for MTBE in surface waters and ground waters, with particular emphasis on drinking water supplies. Additionally, the Lawrence Livermore National Laboratory has also conducted a survey of MTBE in ground water, and the Department of Health Services requires periodic monitoring of MTBE in drinking water supplies as an unregulated contaminant. At this point the potential threat to ground and surface waters from leaking storage tanks, pipelines, recreational vehicles and incidental spills is well recognized and appreciated.

Comment 6: ".. it is also of great concern to me that OEHHA report relies so heavily on studies underwritten by those who benefit from the continued use of this hazardous chemical. Such research must be balanced with sufficient studies from those who do not have a vested interest in the outcome."

Response 6: OEHHA uses data available from independent researchers as well as from industry-sponsored researchers. OEHHA scientists conduct independent assessments of any study data and protocol design, and then determine how much reliance to place on any one study. With respect to our MTBE assessment, we received the most criticism for using data from an independent study by Belpoggi et al. (1995, 1997, 1998) which we determined was conducted and reported in a way that we should consider it in quantitative risk assessment.

Comment 7: "I fear that MTBE has spread farther than any of us realize. We cannot see beneath the ground. This is a silent toxin which spreads and moves each day. MTBE contamination and resultant human illness are not the legacy we want to bequeath to tomorrow's California. Again I strongly urge that the suggested 14 ppb be lowered. We should err on the side of safety and assure that we have not jeopardized the health of Californians."

Response 7: OEHHA appreciates the concern expressed in this comment. We can assure you that we have carefully evaluated the data on MTBE. The procedures we have used for calculating the MTBE PHG, as well as other PHGs, have been developed to protect the health of Californians. Most of the comments we have received on our MTBE PHG proposal and support document indicate that we have erred on the side of public health safety especially in comparison to other levels proposed by other agencies or experts. OEHHA believes that in passing the California Safe Drinking Water Act of 1996, the Legislature meant to promote the adoption of health-protective goals for drinking water in the State. That statute provides detailed specifications for the adoption of public health goals. OEHHA has followed those specifications in proposing the PHG of 13 ppb for MTBE.

Comment 8: "…the growing evidence of adverse health effects experienced by Californians and other people across the nation who have been exposed to MTBE is absent from the report. In the absence of definitive human studies, OEHHA cannot afford to ignore anecdotal stories of Californians whose health has been impacted by MTBE. I fear these are the beginning of a wave of illness we can expect if we do not remove MTBE from our water and our air."

Response 8: OEHHA appreciates you concern about potential health effects of MTBE. OEHHA must base its decisions and recommendations on the best scientific information available usually from the peer reviewed scientific and medical literature. Anecdotal information on MTBE exposures and effects is not usually suitable for the basis of risk assessment as conducted by OEHHA. However such information is not ignored and can occasionally provide leads for well designed epidemiological studies conducted by OEHHA, DHS, or by academic scientists.

Comment 9: "I am concerned about a human health study showing MTBE negatively impacts the white blood cells in humans. Such an effect not only has an impact on cancers, but a host of other health problems."

Response 9: OEHHA presumes this comment refers to the published work of Mordechai et al. (1997) and Vojdani et al. (1997b) cited in the PHG technical support document. These authors reported reversible but statistically significant increased rates of programmed cell death (apoptosis) and cell cycle progression in peripheral blood lymphocytes in 20 Southern California residents exposed to MTBE and benzene contaminated water compared to 10 healthy control human subjects. While apoptosis is a normal process of maintaining healthy cell populations the effects noted in the study appeared to be abnormal. As with other reports on adverse effects of MTBE in human subjects, this study is complicated by simultaneous exposure to benzene, a known blood toxicant and carcinogen. As noted elsewhere in these responses, OEHHA does not expect adverse effects in populations exposed to 13 ppb or less MTBE in tap water by all anticipated routes of exposure. The question of potential synergism between MTBE and other gasoline components is open and will require further scientific data in order to adequately address it.

Comment 10: "Two years ago, I was showing my young grandson how to clean greasy car parts. I put on rubber gloves, picked up the greasy car part and began to wash it in the gas as I have done for more than half a century. To my surprise, the gloves disintegrated in my hands after using the gasoline with MTBE. I washed my hands throughly. That evening I attended a function and my face was covered with red blotches."

Response 10: Apparently gasoline with MTBE has a greater solvent ability for certain types of rubber. Dermal absorption of MTBE from water, while predicted to be low to insignificant in environmental exposure models, may be much higher in the exposure situation of direct contact of MTBE containing gasoline with the skin surface. Individuals react differently to low level exposures that may have little obvious toxic effects. It has been reported (Vojdani et al., 1997a) that seven of 24 gas station attendants, presumably exposed to MTBE during their routine job duties, developed antibodies for MTBE indicating an immune response to MTBE exposure. The reaction of red blotches on the face may have been an immune response to MTBE or another gasoline component although it is difficult to be certain of this without additional testing by a physician or a specialist.

Comment 11: "I urge OEHHA to include in their consideration the effects of MTBE on the health of residents of the small Kern County community of Glennville, where high levels of MTBE have been detected in a number of private drinking water wells in homes and local businesses. People have become ill since their exposure. Residents have suffered from higher rates of cancer and other illnesses since their exposure to MTBE. There have been some cases of

epilepsy which may be associated with their exposure to MTBE. Residents in Elmira have also suffered from a variety of illnesses since a pipeline rupture. In that community, people have developed cancers and other illnesses."

Response 11: OEHHA received at least one call from a concerned resident of Glennville reporting high concentrations of MTBE in contaminated tap water from a private well. OEHHA staff advised the resident to consult a private physician with respect to health complaints and gave advice on reducing MTBE exposure via drinking and showering. We understand that the contamination is the result of leakage from defunct gasoline service station and that other state departments may be involved in remediation of the contaminated site.

With respect to the claims of higher cancer rates, these do not appear credible in view of the relatively limited exposure periods and relatively small populations exposed. Cancer is a chronic disease requiring years of continual low level exposure or years following briefer exposures to potent carcinogens. OEHHA's MTBE risk assessment, albeit based on animal data, indicates lifetime theoretical cancer risks of one in a million at 13 ppb in tap water. These risks may extrapolated somewhat at low exposures, e.g., to one in ten thousand lifetime risk at 1.3 ppm MTBE. The estimates assume 70 years continuous exposure at 3 liters equivalent of water intake per day. While it is difficult to make accurate predictions of the strength of a carcinogen and its target sites in humans based on data in animals, the current data would indicate that MTBE is probably a weaker carcinogen for humans than other carcinogens that commonly contaminate water e.g., trichloroethylene, perchloroethylene, arsenic. Since the lifetime cancer incidence in any population is about 25% it would not be unusual to observe cancers in any exposed population. In order to associate cancers with MTBE exposures one would need to study similar populations that had similar exposures except for MTBE. Normally such epidemiological studies involve hundreds or thousands of subjects and are often inconclusive due to the difficulty of controlling interfering factors. To date there has been no credible study indicating an association of MTBE exposure and cancer in humans.

The association of MTBE exposure and other claimed human health effects suffers from a similar lack of conclusive controlled scientific study. While OEHHA must rely on the best science in developing risk estimates and margins of exposure for carcinogenic and non-carcinogenic water contaminants, respectively, we do not wholly ignore indications of adverse effects that are not yet fully established. Such indications and concerns play a role in uncertainty factors that risk assessors use in developing margins of exposure (MOEs) for water contaminants.

Association of California Water Agencies (ACWA); City of Oceanside, Water Utilities Department; City and County of San Francisco, Public Utilities Commission (7/13/98)

Comment 1: "ACWA believes that OEHHA has incorrectly and inappropriately used a higher daily water consumption rate of 3 liters per day than the normal default rate of 2 liters per day."

Response 1: This comment is similar to those by the Cal-Nev AWWA and WSPA. Please note the respective responses given above. Since the late 1980's OEHHA has used multi-route exposure values (liter equivalents/day) for the large majority of volatile organic chemicals (VOCs) in drinking water. These evaluations were included in supporting documentation for

proposed maximum contaminant levels (PMCLs) which are the basis of many current state MCLs. ACWA is correct in noting that U.S. EPA does not attempt to correct for dermal and inhalation exposures via showering, bathing, flushing toilets, etc. U.S. EPA considers that the relative source contribution default is sufficiently protective for both sources (i.e., food, air, water) and routes (i.e, ingestion, inhalation, dermal). However, the importance of multi-route exposures to VOCs has been amply demonstrated with a number of chemicals in human subjects. OEHHA is not bound to adopt U.S. EPA methodology, particularly where we determine it is inadequately protective of public health in the context of state mandates for public health goals. As indicated above, in a few cases we have chosen not to apply multi-route exposure values. These cases will be reevaluated as more data become available.

Comment 2.: "OEHHA has consistently, and ACWA believes incorrectly, indicated that adoption of PHGs has no regulatory impact…..ACWA has advised OEHHA that PHGs have significant regulatory impact on drinking water suppliers in California and potentially on California businesses and citizens through increased water rates…..ACWA recommends that OEHHA reevaluate the process they have used and adhere to the appropriate Administrative Procedures [sic] Act requirements in developing and adopting PHGs."

Response 2: This comment is similar to that received from Cal-Nev AWWA. Please note also the respective response above. OEHHA's process for PHGs is dictated by statutory mandates and language (Health and Safety Code, Section 116365c) to the effect that PHGs cannot be enforced and hence are not "regulations." More importantly, perhaps, an interested party, Eastman Corporation, filed a lawsuit (Eastman v. Rooney, et al.) contending that PHGs were regulations and thus subject to the Administrative Procedure Act. However, the court ruled that the PHGs were <u>not</u> enforceable and thus <u>not</u> regulations subject to the <u>Administrative Procedure Act</u>. Rather, it is the Maximum Contaminant Levels (MCLs) set by the Department of Health Services (DHS) that are the enforceable regulatory standards. The court confirmed OEHHA's interpretation of the applicable statute (Section 116365c).

Comment 3: "…we are concerned that the United States Environmental Protection Agency (EPA) looked at the exact same studies as OEHHA and concluded in their Drinking Water Health Advisory for MTBE that: 'The carcinogenicity data support a conclusion that MtBE poses a potential for carcinogenicity to humans at high doses. *The data do not support confident quantitative estimation of risk at low exposure…..(*emphasis added).' ACWA recognizes that OEHHA is not bound to follow the actions of EPA. However, we anticipate potential confusion on the part of public water systems and their customers regarding this significant difference in approach."

Response 3: See also the response to comments received from U.S. EPA above. It is true that OEHHA took a different approach from U.S. EPA not only in the adoption of a default linear low dose response extrapolation but also in the use of PBPK modeling for route to route extrapolation. Even with all these differences in methodology applied to the same data, the range of values developed are quite similar, 20-40 ppb for U.S. EPA and 13-47 ppb for OEHHA. ACWA should realize that U.S. EPA Health Advisories have no specific mandate and are provided by U.S. EPA as a public service. The federal standards more specifically analogous to the PHG are the MCLGs. U.S. EPA has not proposed a MCLG for MTBE and is not expected to do so for several years. Thus there will be no federal MCLG to compare with the California PHG for MTBE when adopted by OEHHA. Also the U.S. EPA's range of values attempts to

include the properties of a secondary standard and is described as a "Provisional Health and Consumer Acceptability Advisory for Methyl Tertiary-Butyl Ether (MtBE)." The PHG is defined by law as solely based on human health considerations.

City of Riverside (7/13/98)

Comment 1: "The 1996 amendments to the Safe Drinking Water Act requires peer reviewed science, i.e., "good science" in setting maximum contaminant level (MCL). We are not aware of any peer reviewed science that suggest the use of 3 liters, most especially given the increasing use of bottled water in the state."

Response 1: The law defining PHGs is the California Safe Drinking Water Act of 1996. In that statute the statement that "OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden" has generally been interpreted as requiring assessment of exposures via different sources such as food, water and air as well as to different routes from drinking water (ingestion, inhalation, dermal). It is a well established fact that volatile organic chemicals contaminating drinking water can result in significant inhalation and dermal exposures from showering, bathing, flushing of toilets and other household uses of tap water, as well as ingestion. For over 10 years OEHHA has considered such exposures based on peer reviewed publications of such exposures or use of a peer reviewed environmental model to estimate in house exposures by route (i.e., CalTOX). These multiroute exposures are usually expressed as liter equivalents (Leq) per day. In the case of MTBE the value is 2 liters for ingestion and 1 liter equivalent for inhalation or 3 Leq/day total (the model predicts negligible dermal uptake). Values for typical VOCs evaluated previously range from 5 to 30 Leq/day so MTBE is at the lower end of the range, a reflection of its high water solubility. A few years ago U.S. EPA determined VOC exposure via showering was about equal to that via ingestion and suggested a default inhalation exposure value of 2 Leq/day based on the average of several VOCs (U.S. EPA, Guidance for estimating exposure to VOCs during showering, Risk Assessment Forum, 7/10/91). Thus OEHHA's estimate is only about 75% of this unofficial U.S. EPA default which would translate to a total of 2 + 2 = 4 Leq/day. Bottled water is regulated by the federal Food and Drug Administration and the California Department of Health Services. Bottled water meets or exceeds primary drinking water standards and in many cases is simply processed municipal tap water. The consumption of bottled water may reduce exposure to certain water contaminants via the oral route but there is as yet insufficient information on the occurrence and effectiveness of removal of MTBE from bottled water supplies.

Comment 2: "We are concerned about the regulatory impacts of the proposed PHG for MTBE on California water utilities. We request that OEHHA use peer reviewed science in setting a PHG for MTBE because it will be the starting point for the state MCL for MTBE."

Response 2: While the law does not require peer review of PHG technical support documents, the California Environmental Protection Agency has a policy of seeking peer review on selected PHGs which are expected to be controversial or which have novel methodology. The MTBE draft was peer reviewed by two experts in California's university system prior to its public release in April, 1998. These peer reviewers were in general agreement with our methodology and conclusions. OEHHA reviews all relevant information on the toxicity and human risk of

MTBE and other water contaminants it is evaluating. We cannot limit our review to only peer reviewed materials but attempt to assess the value and reliability of all documents and data we employ in our risk assessments. The commenter might review other comments and responses above to see the range of issues and concerns raised.

Orange County Water District (OCWD) (7/13/98)

Comment 1: "OCWD is concerned that OEHHA has used 3 liters per day as the average daily water consumption in the health risk assessment to determine a PHG. OCWD urges OEHHA to use 2 liters per day as the consumption rate factor in the calculation of PHG for MTBE."

Response 1: The law defining PHGs is the California Safe Drinking Water Act of 1996. In that statute the statement that "OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden" has generally been interpreted as requiring assessment of exposures via different sources such as food, water and air as well as to different routes from drinking water (ingestion, inhalation, dermal). It is a well established fact that volatile organic chemicals contaminating drinking water can result in significant inhalation and dermal exposures from showering, bathing, flushing of toilets and other household uses of tap water, as well as ingestion. For over 10 years OEHHA has considered such exposures based on peer reviewed publications of such exposures or use of a peer reviewed environmental model to estimate in house exposures by route (i.e., CalTOX). These multiroute exposures are usually expressed as liter equivalents (Leq) per day. In the case of MTBE the value is 2 liters for ingestion and 1 liter equivalent for inhalation or 3 Leq/day total (the model predicts negligible dermal uptake). Values for typical VOCs evaluated previously range from 5 to 30 Leq/day so MTBE is at the lower end of the range, a reflection of its high water solubility. A few years ago U.S. EPA determined VOC exposure via showering was about equal to that via ingestion and suggested a default inhalation exposure value of 2 Leq/day based on the average of several VOCs (U.S. EPA, Guidance for estimating exposure to VOCs during showering, Risk Assessment Forum, 7/10/91). Thus OEHHA's estimate is only about 75% of this unofficial U.S. EPA default which would translate to a total of 2 + 2 = 4 Leq/day.

Comment 2*: PHGs will have a significant regulatory impact contrary to OEHHA's statements.* (Paraphrased)

Response 2: OEHHA is mandated to *not* consider costs in the adoption of the numerical value of the PHG. Costs and technical limitations are considered by DHS in developing the MCL. The PHG is only one of the factors it considers, albeit an important one.

Oxygenated Fuels Association, Inc. (OFA) (7/13/98)

Comment 1: "OFA has evaluated this draft PHG, and concluded that (1) the proposed 47 ppb PHG is somewhat overly protective of human health, (2) the proposed PHG of 14 ppb level is not defensible based on the strength of all the scientific evidence, and (3) a scientifically defensible concentration for MTBE in tap water is 70 ppb to protect against all forms of toxicity, based on the strength of evidence of the entire body of scientific evidence."

Response 1: (a) OEHHA considered the "entire body of scientific evidence" in its risk assessment of MTBE for drinking water. OEHHA concludes that there is insufficient evidence to confidently assume modes of action for the various cancers induced by MTBE in rodents and potentially in humans. OEHHA used both non-carcinogenic and carcinogenic endpoints in calculating MTBE concentrations in drinking water that we determined would not be associated with significant risk of adverse human health effects over a lifetime of exposure. These values differed by only a factor of three. In our view the uncertainty about the mode of action of MTBE in causing so many different tumors by different routes of exposure in rodents requires that our decision regarding MTBE in drinking water be *more* protective of public health rather than less protective. Therefore, the PHG of 13 ppb provides the most pubic health-protective value, the development of which, is mandated by law (Health and Safety Code, Section 116365).

(b) The value of 47 ppb OEHHA calculated was based on increased relative kidney weights in the Robinson et al. (1990) 90-day gavage study in rats. This is the same study used by U.S. EPA in their evaluations of MTBE. The only difference in OEHHA's calculation based on this study is our assumption of some potential exposure to MTBE via the inhalation route in the home due to showering, bathing, flushing toilets etc.

(c) As noted in (b) above the only difference between our calculation and that of U.S. EPA is in the assumption of 1 Leq/day additional household exposure via the inhalation route. Therefore U.S. EPA's calculated value of 70 ppb when multiplied by 2/3 becomes 47 ppb. The law defining PHGs is the California Safe Drinking Water Act of 1996. In that statute the statement that "OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden" has generally been interpreted as requiring assessment of exposures via different sources such as food, water and air as well as to different routes from drinking water (ingestion, inhalation, dermal). It is a well established fact that volatile organic chemicals contaminating drinking water can result in significant inhalation and dermal exposures from showering, bathing, flushing of toilets and other household uses of tap water, as well as ingestion. For over 10 years OEHHA has considered such exposures based on peer reviewed publications of such exposures or use of a peer reviewed environmental model to estimate in house exposures by route (i.e., CalTOX). These multiroute exposures are usually expressed as liter equivalents (Leq) per day. In the case of MTBE the value is 2 liters for ingestion and 1 liter equivalent for inhalation or 3 Leq/day total (the model predicts negligible dermal uptake). Values for typical VOCs evaluated previously range from 5 to 30 Leq/day so MTBE is at the lower end of the range, a reflection of its high water solubility. A few years ago U.S. EPA determined VOC exposure via showering was about equal to that via ingestion and suggested a default inhalation exposure value of 2 Leq/day based on the average of several VOCs (U.S. EPA, Guidance for estimating exposure to VOCs during showering, Risk Assessment Forum, 7/10/91).

Comment 2*:* "MTBE is not genotoxic in numerous assays capable of detecting the major forms of genotoxicity, and, therefore, it is not likely to be a genotoxic carcinogen in animals or humans. Therefore, the use of linear extrapolation to estimate cancer potency is not justified."

Response 2: We accept that MTBE is probably not genotoxic as indicated in the various assays conducted to date. However lack of genotoxicity does not establish the mode of carcinogenic action. Because there is no clear mode of action indicated for the carcinogenic action of MTBE observed in the three animal studies evaluated, OEHHA has used a default approach of linear extrapolation as recommended in U.S. EPA's 1996 proposed Guidelines for Carcinogen Risk

Assessment (U.S. EPA, Federal Register, Vol. 61, No. 79, Tuesday, April 23, 1996, 17960-18011). This is explained at some length in the technical support document and was also covered at length at the MTBE workshop held in Berkeley on 5/15/98.

U.S. EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment (1996) provide sufficient latitude for the selection of the linear approach to carcinogen potency calculations: "The default assumption of linearity is also appropriate as the ultimate default when evidence shows no DNA reactivity or other support for linearity, but neither is it sufficient evidence of a nonlinear mode of action to support a nonlinear procedure." It should also be noted that U.S. EPA identifies three defaults: linear, nonlinear, and linear plus nonlinear. Thus the decision on which option is chosen depends not only on the weight of evidence but also on the statutory mandate in question. In general, OEHHA considers the linear approach to be the most health conservative and to be used when there is insufficient information supporting a specific mode(s) of action or there is clear evidence supporting the linear approach, followed by both linear plus nonlinear, where there is equivocal evidence supporting either approach, and finally nonlinear when there is a preponderance of evidence supporting a nonlinear approach

Comment 3: "MTBE is not a of the carcinogenic property of other chemical carcinogens; therefore, the use of linear extrapolation to characterize toxic potency is not justified."

Response 3: In the one promotion study published to date, MTBE appears to lack the ability to promote liver tumors initiated by N-nitrosodiethylamine in mice. OEHHA decided not to include the mouse liver endpoint in its CSF estimate.

Comment 4: "MTBE at high doses has produced tumors in laboratory animals as a result of processes not applicable to humans exposed to low doses of MTBE in water, air, or both. Therefore, the most appropriate method of defining cancer potency is the Margin of Exposure (MoE). Consequently, no cancer hazard exists for humans to MTBE at background levels in tap water in California."

Response 4: The mechanisms by which MTBE increases the incidence of tumors in animals and could potentially be carcinogenic in humans has not yet been established. Ongoing research projects may produce useful insights, but at present OEHHA scientists are not convinced that the proposed processes are clearly evident. The MOE approach to assessing carcinogenic risks of MTBE exposure to human populations was conducted by U.S. EPA (1997) and resulted in MOE values ranging from 40,000 to 550,000 for a 20 μg/L MTBE drinking water concentration. We believe these figures are in reasonable agreement with OEHHA's 1E-6 extra lifetime cancer risk value of 13 μg/L.

Comment5: "Male rat kidney tumors are likely to result from secondary, non-genotoxic tissue damage caused by otherwise highly toxic doses of MTBE – doses unlikely to be experienced by humans; and this mechanism is unlikely to exist in humans."

Response 5: OFA has proposed that kidney tumors in rats exposed to MTBE occur only following deposition of α_{2u}-globulin in the kidney cells. This proposed mode of action for MTBE induced kidney tumors has been argued at great length and there is some difference of opinion among scientific experts on this point. OEHHA scientists have reviewed all the information available on this question and found that the available data on renal tumorigenesis

indicate that MTBE induces only mild accumulation of the α_{2u}-globulin protein and only mild or partial expression of α_{2u}-globulin associated nephropathy in male rats, while clearly exacerbating the expression of non-α_{2u}-globulin rat nephropathy in both male and females (NSTC 1997). Thus, based on the available evidence, only one of the three criteria established by U.S. EPA (1991) for causation of an α_{2u}-globulin effect has been met in the case of MTBE induced renal carcinogenesis in male rats. Since only one of the criteria has been met it does not appear that the scientific evidence supports a conclusion that the male rat kidney tumors are likely to result from secondary non-genotoxic tissue damage. The commenter did not mention the U.S. EPA criteria for evaluating mechanistic data with respect to male rat kidney tumors

Comment 6*:* "Female mouse liver tumors are the result of high, non-genotoxic doses of MTBE interfering with the tumor suppressor mechanisms of estrogen in female mouse liver-mechanisms that are not likely to be present in human liver."

Response 6: While this is an interesting concept, the evidence provided by OFA is insufficient in our view to support it. The studies cited, e.g., Casanova & Heck (1997) on DNA-protein cross-links and RNA-formaldehyde adducts arising from MTBE metabolism, suggest that the formaldehyde metabolite of MTBE is probably not involved in the induction of liver cancer in mice. These data and others cited still do not indicate what is involved in the carcinogenic mode of action. Also, it might be useful to note that hepatocellular carcinomas were found at the high dose in male mice. Due to the lack of specific evidence, OEHHA has assumed the parent compound, MTBE, is the cause

Comment 7: "The evidence suggests that the testicular tumors in rats were likely to result from factors other than MTBE."

Response 7: The studies cited by OFA are not sufficient for OEHHA to discount these tumors as being of potential relevance to human health effects resulting from continued exposure to low levels of MTBE. Testicular tumors were noted in two separate studies, in two strains of rats, by two routes of administration. The commenter discounts the testicular tumors observed in the Bird et al. (1997) study yet a clearer dose response is seen in the Belpoggi et al. (1998) study. While the relevance of almost any animal tumor to humans can be debated with respect to the probability of strict concordance of sites between species, which is generally low, the observation of this tumor in both the Belpoggi et al. and Chun et al. studies adds weight to the finding and supports the veracity of both studies. OFA has argued that all of the observed tumors while not artifacts are irrelevant to human cancer risk assessment based on interesting but incomplete evidence. OEHHA concluded that it is unlikely that all of these tumors can be irrelevant particularly when a plausible mode of action for any one of them is considered lacking.

Comment 8: "OEHHA should acknowledge that the lifetime gavage of MTBE is not scientifically appropriate to characterize cancer hazard or to estimate cancer risk for humans."

Response 8: OEHHA does not agree that gavage studies of MTBE or other chemicals give data that are not appropriate for use in human cancer risk assessment. Obviously it would be desirable to have a lifetime drinking water study, and OFA might consider this if future work is planned for MTBE. However, we believe that the inhalation and gavage studies with PBPK dose

modeling give reasonable estimates of appropriate dose metrics for cancer risk assessment. Furthermore, the Belpoggi et al. (1998) follow up study provides significant additional information and clarifications on the tumor types observed, related histopathology, and revised tumor incidences. Our revised PHG technical support document provides a review of these new data and updated calculations which include them.

Comment 9: "OEHHA should use U.S. EPA's evaluation of the cancer data on chloroform as a template to judge that a sufficient weight-of-evidence exists to consider that MTBE is not a cancer hazard or risk to humans exposed at low doses in all media."

Response 9: OEHHA has not yet fully evaluated U.S. EPA's work on chloroform but will do so in the course of development of the PHG for total trihalomethanes. At this point it is premature to make direct comparisons between MTBE and chloroform, a carcinogen which has been studied in depth for over a decade and which has been the subject of previous peer-reviewed health risk assessments by OEHHA and U.S. EPA. Presently U.S. EPA's risk assessment approach for chloroform is still undergoing review and is not yet final.

Comment 10: "OEHHA incorrectly states that none of the assays can detect gene mutations; however the TA strains of Salmonella are quite capable of making such an identification, have a false negative rate as a group that is quite low for in vitro tests, and have identified no gene mutations or chromosome damage caused by MTBE."

Response 10: OEHHA is fully aware of the capabilities and limitations of the Ames Salmonella/mammalian microsome test for genetic toxicity, especially for volatiles such as MTBE. The text has been revised to improve the clarity of this fact.

Comment 11: "OEHHA cited positive results in the activated mouse lymphoma assay (questioned as suitable assay because of its unique sensitivity to mutagens: Preston, 1998), and attributed the findings to formaldehyde (CHOH) which it called a "major" metabolite. Actually HCOH is a minor metabolite even when large doses of MTBE are administered, as indicated by a human study that found MTBE (the largest amount), TBA, formate, and methanol as excretion products but not CHOH."

Response 11: The commenter is correct and the PHG technical support document has been revised to remove the "major."

Comment 12: "If OEHHA were to adjust its calculation for PHGs for the proper volume of water consumed per day, its PHG for non-cancer effects would change from 47 to 71 ppb. This conclusion is supported by OEHHA through their citation of the study by Brown (1997) which noted the arithmetic mean for residential exposures to MTBE by inhalation were estimated to be between from 0.4 and 0.6 μg/kg-day. Further, Brown noted that 98.5% of the U.S. population living in MTBE-using areas uses water with concentrations affected only by atmospheric deposition, if at all, and these concentrations are below current levels of detection (< 2μg/liter)."

Response 12: Actually since the 47 ppb is a rounded number the value without allowance for household inhalation exposures would be 70 ppb. The rationale for using 3 Leq/day instead of 2L/day was discussed in response 1c above. Estimates of MTBE exposure in the U.S. population while useful for comparison may not be fully indicative of the range of exposures in California. The data on MTBE are still being collected and evaluated but early analyses of exposure of Californians to MTBE detailed in the University of California report (M.L. Johnson, Exposure of humans to MTBE from drinking water, In: Health and Environmental Assessment of MTBE, Report to the Governor and Legislature of the State of California as Sponsored by SB 521, November 12, 1998) indicate that 40% of the population would be exposed to doses of MTBE higher than indicated by the OEHHA proposed PHG of 14 ppb (6.8×10^{-4} mg/kg-d). The UC study, which included a probabilistic analysis, indicated a negligible risk concentration of 5 ppb although their main recommendation was 10 ppb (one significant figure) based on a deterministic analysis. Thus a more detailed exposure assessment for Californians indicates that OEHHA's estimates are not overly conservative.

Comment 13: "OEHHA states that 'lymphomas and leukemias of the Sprague-Dawley rat commonly arise from a similar cell origin, in which case the aggregation of these tumors for carcinogenic identification and risk assessment purposes is appropriate' (Other Relevant Data, Pathology, para.1.). Even if that were true for the Sprague-Dawley rat, the current theory for differentiation of the hematopoietic cells clearly distinguishes the lymphoid from the myeloid tissues. NO evidence for this conclusion is presented, and the conclusion is contrary to the NTP. OEHHA should provide sound justification for its conclusion."

Response 13: The comment is mistaken in interpreting OEHHA's statement as implying that lymphoid and myeloid tissues are to be considered together. The leukemias referred to in this case are all of lymphoid cell origin. This point has been extensively discussed with respect to the specific types of tumors seen in the MTBE study, and the conformance of their diagnosis with NTP criteria, by Belpoggi et al. (1998) in their recent reanalysis, as well as by NTP scientists, and by OEHHA in other analyses and responses. Belpoggi et al. (1998) confirmed that, as expected, these neoplasias were of lymphoid origin. Specifically, these tumors were classified as lymphoblastic lymphomas, lymphoblastic leukemias, and lymphoimmunoblastic lymphomas. These three tumor types are classified by IARC (1993) as malignant lymphomas. Note that these tumors are entirely distinct from the mononuclear cell leukemias commonly observed in the Fischer rat, which should not be combined with other leukemias/lymphomas (McConnell et al., 1986).

Comment 14: "OFA finds, upon careful evaluation of the draft PHG, that OEHHA has failed to apply the premises incorporated in the USEPA guidelines resulting in erroneous conclusions."

Response 14: OEHHA rejects this claim of erroneous conclusions. First, U.S. EPA's 1996 guidelines for carcinogen risk assessment have not yet been finalized by U.S. EPA. Secondly, OEHHA has used some of the concepts and approaches given in the draft guidelines in this risk assessment and in others conducted over the past few years. Please also note response to comment 2.

Comment 15: "The toxicokinetics of t-butyl alcohol appear to be far more complex than those of MTBE. With a quantitative description of the important determinants of MTBE and t-butyl alcohol dosimetry understood, a better assessment of the potential toxic and cancer risk for humans exposed to MTBE can be made."

Response 15: OEHHA agrees with this statement in general. MTBE toxicokinetic models do not predict the metabolism and excretion of TBA well. Also OEHHA believes human kinetic models of MTBE are not yet sufficiently well grounded in human metabolic data. However there is currently insufficient evidence that any of the metabolites of MTBE are causally related to tumor induction in MTBE exposed experimental animals. Thus in our risk assessment OEHHA has assumed that the parent compound, MTBE, is the putative carcinogen. Under current California statute OEHHA is required to update PHG assessments at least every five years.

Comment 16: "OEHHA cites the respected authority ACGIH as having defined MTBE as A3 Animal carcinogen (Introduction, para 6, line 1). OEHHA failed, however, to note that the definition for this category means that ACGIH has concluded MTBE is not likely to be a human carcinogen in the workplace where repeated and prolonged exposures may be higher than those in the general population via water or air or the contamination of the two."

Response 16: We have added the ACGIH definition to the Introduction (p. 4) of the document. OEHHA can not be as confident as ACGIH about the likelihood of non-carcinogenicity of MTBE in exposed human populations. Workers in occupational situations may respond differently to MTBE than community populations that include children, the elderly, and in general a broader range of individuals with varying susceptibility to the adverse effects of toxic chemical exposure.

Comment 17: "Furthermore, OEHHA (page 51) incorrectly and incompletely quoted from Dr. Mennear's paper on MTBE, and thus provided an unbalanced perspective on his interpretation of the carcinogenicity data. OEHHA seems to have converted the statement "The mechanism of these apparently sex-specific tumors has yet to be established" to mean in OEHHA's words "the mode of action remains unknown." OEHHA overlooked that Dr. Mennear went on to say "Their localization and spectrum of microscopic changes are highly suggestive of a pattern of chronic renal tubular toxicity with cell death and reparative cell proliferation." Clearly, Dr. Mennear intended to indicate that a definitive mode of action was indeed known confidently."

Response 17: OEHHA did not quote Dr. Mennear directly and we did not "overlook" this statement. We just didn't attach sufficient importance to it to discuss or acknowledge it explicitly. The actual OEHHA statement in the Summary of the Evidence section (p. 64) is: "The mechanism by which MTBE induces tumors at multiple sites in animals remains unknown (NSTC 1997, Mennear 1995, 1997a, 1997b)." This refers to all the tumors induced by MTBE not simply the male rat kidney tumors referred to in the Mennear quote in the comment above. OFA may believe that a "suggestive pattern" represents a "confidently known, definitive mode of action" for the kidney tumor site. However, in so doing they overlook the usual conventions of the English language.

OEHHA's conclusion that there is no definitive mode(s) of action (MOA) for any of the four cancers induced by MTBE does not rely solely on the cited papers of Dr. Mennear and these papers are cited as sources of additional discussion and interpretation. For example from the 1997b paper with regard to the hepatocellular adenomas we find the following: "Although a mechanism to explain the effect is not readily apparent a hormonally mediated effect is likely since only females were affected" and "Despite the absence of an unequivocal explanation for a

hormone determination of the mouse hepatocellular adenomas, recent experimental evidence supports the hypothesis." OFA may take these quotations as a definitive evidence of a hormonal MOA for MTBE-induced liver tumors where OEHHA sees at best equivocal support for a plausible MOA. OEHHA chose not to use the liver site in the calculation of the CSF for MTBE.

The fact is there are no established MOAs for any of the MTBE-induced tumor sites. An examination of the U.S. EPA's 1996 Proposed Guidelines for Cancer Risk Assessment (Federal Register Vol. 61, No. 79, p.17980) reveals what sort of information would support a MOA determination:

- Has a body of data been developed on the agent that fits with a generally accepted mode of action?
- Has the mode of action been published and gained general scientific acceptance through peer-reviewed research **or is it still speculative** (emphasis added)?
- Is the mode of action consistent with generally agreed-upon principles and understanding of carcinogenesis?
- Is the mode of action reasonably anticipated or assumed to operate in humans? Etc.

Cadwalader,Wickersham & Taft (On behalf of the Oxygenated Fuels Association) (7/13/98)

Comment 1: *The OFA participated in the MTBE workshop and submitted detailed comments. Public comments at the workshop were overwhelmingly opposed to the characterization of MTBE as carcinogenic, and to the unreasonably low PHG of 14 ppb.* (Paraphrased)

Response 1: The comments of the MTBE manufacturers, OFA, and the representatives of the regulated community (water utilities) were opposed to the PHG, as noted. Other participants including the City of Santa Monica and Senator Mountjoy did not consider OEHHA's proposal to be overly health protective. Please refer to the comments (and OEHHA responses) above by Communities for a Better Environment and the City of Santa Monica taken from the meeting transcript. Also note the responses to the detailed comments of OFA above. The scientific decisions made in the document are not based on the majority opinion at a public meeting. Also scientific information submitted was evaluated, considered, and incorporated into the document as appropriate.

Comment 2: "Numerous comments were made in these regards pointing out defects in the scientific methodology upon which the proposed PHG was based. Nevertheless, in June 1998 OEHHA issued the Draft PHG technical support document that ignores the substantive criticisms previously made. The draft PHG also ignores the public comments concerning the mischaracterization of MTBE as a carcinogen, and the unreasonable onus of a PHG set as low as 14 ppb."

Response 2: OEHHA reviewed all comments received and made a number of changes suggested by MTBE workshop attendees and others, notably in the risk characterization and in providing a more detailed description of the uncertainties of the assessment. OEHHA has not ignored any criticisms provided regarding the MTBE document. We considered each comment and evaluated each comment on its scientific merit. The PHG document is not primarily a

carcinogen classification vehicle; rather, OEHHA evaluates data on all toxic endpoints and bases the PHG on a health protective level, as is mandated by the law. OEHHA believes it has addressed all substantive scientific comments. OEHHA has defined in the document how it arrived at its conclusion regarding sufficient evidence for the carcinogenicity of MTBE in animals and potentially in humans. It is not clear, however, how OFA would define a carcinogen based on data in animals. Therefore, we can not respond to its charge that OEHHA (and several other scientific organizations) have "mischaracterized MTBE as a carcinogen." The PHG of 13 ppb is higher than MCLs previously promulgated for many carcinogens detected in California drinking waters so it is not clear to what "onus" the commenter is referring.

Comment 3: "By calculating a PHG using linear extrapolation, the Draft PHG fails to use the most current principles, practices, and methods that would be properly applicable, etc…..In accordance with EPA Risk Guidelines, linear extrapolation is only appropriate for substances for which there is evidence of linear human cancer potential at low doses."

Response 3: U.S. EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment (Federal Register 61:17981 (1996) provide sufficient latitude for the selection of the linear approach to carcinogen potency calculations: "The default assumption of linearity is also appropriate as the ultimate default when evidence shows no DNA reactivity or other support for linearity, **but neither is it sufficient evidence of a nonlinear mode of action to support a nonlinear procedure**(emphasis added)." It should also be noted that U.S. EPA identifies three defaults: linear, nonlinear, and linear plus nonlinear. Thus the decision on which option is chosen depends not only on the weight of evidence but also on the statutory mandate in question. In general, OEHHA considers the linear approach to be the most health conservative and to be used when there is insufficient information supporting a specific mode(s) of action or there is clear evidence supporting the linear approach, followed by both linear plus nonlinear, where there is equivocal evidence supporting either approach, and finally nonlinear when there is a preponderance of evidence supporting a nonlinear approach.

Comment 4: "The MTBE PHG is being adopted without the required compliance with the California Administrative Procedure Act."

Response 4: This comment is similar to those received from Cal-Nev AWWA, and ACWA. Please note also the respective responses above. OEHHA's process for PHG development is dictated by statutory mandates and language (Health and Safety Code, Section 116365c) that PHGs are not be enforceable. Therefore, PHGs are not regulations. More importantly, perhaps, an interested party, Eastman Corporation, filed a lawsuit (Eastman v. Rooney, et al.) contending that PHGs were regulations and thus subject to the Administrative Procedure Act. However, the court ruled that the PHGs were <u>not</u> enforceable and thus <u>not</u> regulations subject to the <u>Administrative Procedure Act</u>. Rather, it is the Maximum Contaminant Levels (MCLs) set by the Department of Health Services that are the enforceable regulatory standards. The court confirmed OEHHA's interpretation of the applicable statute (Section 116365c).

Comment 5: "There is no evidence that MTBE is a human Carcinogen"

Response 5: The commenter does not appear to appreciate the differences in the standard of proof required in public health protection vs. chemical tort proceedings. Incidental therapeutic MTBE exposures are insufficient to demonstrate the lack of carcinogenicity of MTBE resulting from chronic low level exposure via drinking water, ambient air and household uses of MTBE contaminated water. OEHHA does not require positive proof of carcinogenicity in humans before developing a PHG based on carcinogenicity observed in experimental animals. In fact most of the chemical carcinogens OEHHA has assessed in the past have relatively little human data and a large majority of cancer risk assessments are based on animal data.

With respect to the claim that OEHHA has critically erred in applying Subsections (c) 2 and (c) 6, OEHHA rejects this claim. Subsection (c) 2 states that "Each public health goal shall be set for a carcinogen or other substance that may cause chronic disease at a level that, based on currently available data, does not pose any significant risk to health." OEHHA interprets this subsection as requiring a determination of negligible risk based on all available data NOT solely available HUMAN data. OEHHA chose a quantitative estimate of negligible cancer risk, namely 1E-6 extra lifetime cancer risk based on an analysis of the animal cancer database to satisfy this requirement.

With respect to subsection (c) 6, OEHHA is uncertain what the commenter is claiming that OEHHA has misapplied. The subsection refers to requirement that OEHHA should apply an adequate margin of safety in setting a PHG that is protective of public health. OEHHA has determined that a concentration in water representing a negligible quantitative cancer risk level fulfills this requirement. Current toxicological practice does not set standards at a threshold level where toxicity begins to take effect. OEHHA interprets this subsection as providing a margin of safety from the threshold value e.g. the LED_{10} when using the nonlinear approach or applying the linear approach with the negligible 1E-6 risk criterion. In the case of MTBE we have chosen the latter approach due to lack of sufficient mechanistic data.

Comment 6: "The risk assessment and the PHG do not use the most current principles, practices, and methods used by public health professionals."

Response 6: OEHHA rejects this erroneous claim. First, U.S. EPA's 1996 guidelines for carcinogen risk assessment have not yet been finalized by U.S. EPA. Second, OEHHA has used some of the concepts and approaches given in the draft guidelines in this risk assessment and in others conducted over the past few years. Third, our draft PHG technical support document was peer reviewed by two experts in the University of California and was reviewed in the context of the University of California Report to the Governor and Legislature on MTBE. Finally, OEHHA has evaluated the animal studies on MTBE in sufficient detail to propose a PHG and supporting documentation exceeding in size that of some 45 other risk assessments for drinking water contaminants conducted over the past two years. On the issue of mechanism of action, OEHHA rejects the OFA claim of the alpha(2u)-globulin mechanism for male rat kidney tumors induced by MTBE. OEHHA has determined that criteria established by U.S. EPA for this mechanism to be operative were not met in the case of MTBE. OEHHA's use of the linear extrapolation does employ U.S. EPA's draft carcinogen risk assessment guidelines. Please refer to the response to comment 3.