Appendix B. Response to Comments

B.1. Peer Review

Peer review was invited from the following individuals:

Dr. Joseph R. Landolph
USC/Norris Comprehesive Cancer Center
University of Southern California

Dr. Alvin Greenberg
Risk Science Associates
San Rafael, CA

Dr. Catherine VandeVoort
California Regional Primate Research Center
University of California, Davis.

In this Appendix, the comments of the peer reviewers (with the exception of Dr. VandVoort - see page B-24) are provided followed by OEHHA's responses to those comments.

B.1.1. Comments of Dr. Landolph

Peer review comments from Prof. J.R. Landolph primarily address the risk characterization of the pollutants of concern that will be emitted under various fuel scenarios. These fuel scenarios include MTBE-containing fuel based on the 1997 emission inventory, and MTBE-containing fuel, ethanol-containing fuel (both 2% and 3.5% ethanol fuel scenarios), and non-oxygenated fuel based on predicted 2003 emissions. The comments also address the methodology used for quantifying cancer and noncancer risks, research needs, conclusions, and toxicity summaries in Appendix A. Responses will be made to the 'specific comments', which address in greater detail all the 'general comments' made

General Comments

The stated objective of this report is to evaluate the public health impacts of utilizing ethanol as an oxygenate in gasoline. This report therefore quantitates and summarizes the health risks to humans when various formulations of gasoline are utilized in California, including methyl tertiary butyl ether (MTBE)-based California Phase 2 Reformulated gasoline (CARFG), nonoxygenated gasoline, gasoline containing ethanol with an overall oxygen content of 2%, and gasoline containing ethanol with an oxygen content of 3.5%. Health risks quantified included toxicity to the ocular and respiratory systems of humans exposed to these fuels, and the lifetime risk of incurring cancer that would occur in humans exposed to these fuels. The authors evaluated evaporative emissions, tailpipe (exhaust) emissions, and atmospheric transformation products that arise from the use of ethanol in gasoline. The authors utilized data generated by the model from the California Air Resources Board, which included estimates of total air concentrations of various pollutants, identified chemicals of potential concern, and generated a quantitative risk assessment of the health effects that these concentrations of these pollutants could induce in humans. Specifically, the authors generated lifetime cancer risk estimates and also

acute and chronic hazard indices associated with exposure to the separate and total fuel components.

The Chemicals of Potential Concern (COPC) identified included the oxygenates MTBE and ethanol; the combustion products butadiene, formaldehyde, acetaldehyde, and carbon monoxide; the evaporative emittents benzene, hexane, and toluene; and the atmospheric transformation products peroxyacetyl nitrate(PAN) and ozone. These are appropriate choices for the Chemicals of Potential Concern. Perhaps heptane, which is very neurotoxic, should be included in this section as well. They then used health assessment values to determine toxic or carcinogenic risk due to the separate chemicals and to the chemicals in the aggregate, assuming additivity of the risks. They found firstly that for most COPC, the non-cancer hazard Quotients (HQs) were below one, except that the chronic HQ for formaldehyde varied from 1.8 to 2.4, the HQ for acute exposure to PAN varied from 2.3 - 2.4, the HQ for acute exposure to carbon monoxide varied from 1.0 to 1.6, and the HQ for acute ozone exposure varied from 2.5 to 2.7.(Tables 5a and 5b). Clearly, attention needs to be focussed on these values, and they need to be lowered if possible in the future by encouraging more public transportation, use of electric-powered cars, and use of solar-powered cars.

The lifetime cancer risk values for exposure to these fuels and their components varied considerably. For the 1997 MTBE-gasoline formulation, the greatest risks came from benzene (upper risk, 110/million), butadiene (upper risk, 130/million), and formaldehyde (upper risk, 33/million). All these lifetime cancer risks decrease with all four fuel formulations considered (Table 5c). A conclusion that can be drawn is that the lifetime cancer risks are similar with all four fuel formulations, and lower than those that occur with use of the 1997 MTBE fuel formulation. The authors further found that the cumulative cancer risks for each of the four new fuel scenarios decreased from the 1997 MTBE-containing gasoline scenario, and were similar(Table 7). Hence, removing MTBE from the gasoline would certainly improve the environmental situation as regards pollution of the ground water with this chemical, and would lead to cancer risks similar to those induced by the other three fuel scenarios for 2003 (Table 7). The cumulative lifetime risks for cancer from fuel exposure decreased from 280/million in the 1997 MTBE-containing gasoline scenario, to 170 - 190/million for the scenarios using the four types of gasoline in 2003. This is an improvement in the lifetime cancer risk and again indicates that MTBE can likely be removed from the gasoline, and replaced with ethanol, and that the lifetime cancer risk of Californians will not be changed significantly. However, what worries the reviewer is that the lifetime cancer risks still remain too high, and would lead to approximately 190 cancers/million, which would lead to 190 x 30 or 5,700 excess cancers in California due to the use of these fuels. Clearly, some thought should be given to gradually moving to electric-powered automobiles and trucks, to solar-powered automobiles and trucks, and to increased use of public transportation to lower both the HI and lifetime cancer risk values.

Again, for toxicity considerations, Tables 8-10 are very instructive. They indicate that the HQ values for fuel constituents either remain the same or decrease slightly when one considers the 1997 MTBE-gasoline values compared to the 2003 values for the four fuels considered. This again suggests that the MTBE-containing gasoline can likely be replaced with the four fuel scenarios in the year 2003, and the individual and cumulative

HI values will either stay the same or decrease slightly. What is again worrisome is that the cumulative acute HI values range from 6.3 to 6.7 for eye irritation and from 3.6 to 3.8 for acute respiratory irritation, which is too high(Tables 8 and 9). It is further worrisome that the maximum cumulative chronic hazard indices range from 4.8 - 5.0 for respiratory irritation(Table 10). This data indicates that one can replace the 1997 MTBE-gasoline scenario with the four fuel scenarios proposed for 2003 with either the same or slightly decreased cumulative HI values, and one can remove the MTBE from the gasoline and have about the same cumulative HI value in 2003, benefiting from same HI value and eliminating the threat of pollution of water supplies by MTBE. However, it still appears that further reduction in pollution is necessary to lower the cumulative HI values.

I very much enjoyed reading this report. It is clearly written, well-written overall, and comes to firm conclusions. I was very impressed with the Appendix. I actually suggest placing the Appendix under the Section, Chemicals of Potential Concern, Section 2.0. Otherwise, the reader is constantly looking to determine which citations have been made to document the scientific statements that are made in section on Chemicals of Potential Concern, and this is distracting. The conclusions that the authors came to are very reasonable and consistent with the data and calculations they presented.

I agree that the health risks, both for toxicity and for carcinogenesis, are not significantly different between the 2003 formulations of gasoline, whether it contains MTBE, 2% ethanol, 3.5% ethanol, or non-oxygenated gasoline. Hence, from the standpoints of toxicity and carcinogenicity, any of these four formulations should work well. There are slight differences, and I would recommend choosing those formulations that show the lowest human health risk possible, in the interests of the people of the State of California. I also recommend some discussion as to why the 2003 risks are significantly below the 1997 risks in terms of toxicity and carcinogenicity. This was ascribed to lower fuel consumption in 2003. Watching the traffic increase in Los Angeles over time, and knowing the projected population increase in California with time, I am very skeptical about this forecast. Please summarize this consideration, making concise references to the relevant OEHHA documents on this issue, to fortify the conclusions cited about less use of gasoline in 2003, by adding one extra paragraph or so.

Passing from the conclusions in the document on the relative hazards of the four formulations of gasoline, this reviewer is concerned that the cumulative (additive) Hazard Indices are significantly above 1.0 for the chemicals studied, some reaching as high as 6.9 for the 1997 MTBE gasoline acute eye irritation HI value (Table 8, upper bound value). Even for the 2003 values, with the four gasoline formulations, the values range from 6.3 to 6.7, which in my opinion is far too high and erodes the safety margin built into the HI index. Some effort should in my opinion be made to address this situation by lowering the levels of toxic fuel components in the air even further. In Table 9, the cumulative acute HI values for respiratory irritation are also too high, ranging from 3.9-4.0 in 1997 to 3.6 to 3.8 projected in the year 2003. This might present a significant problem for children, athletes who exercise strenuously, and young children. Some attempt should also be made to address this situation in the future.

In addition, the cumulative lifetime cancer risks can be used to show that in California, with 30 million people, there could be as many as 5,100 extra cancers

incurred. In my opinion, these risks are too high, even though I am aware that 32% of the population of the U. S. will eventually contract cancer. This should be more strongly emphasized in the text. This data suggests to me that further efforts should be made to encourage motorists and truck drivers (particularly with the risk from diesel fuel) to convert to electric-powered or solar-powered vehicles, gradually so this does not disrupt the economy, and to convince the people of California to use more public transportation, to reduce the risks of toxicity and carcinogenicity from air-borne gasoline constituents, and to reduce pollution of the water with gasoline constituents, including not only MTBE but also benzene, toluene, xylenes, ethylbenzene, butadienes, and hydrocarbons. This clearly is the wave of the future.

I have made a number of specific suggestions, criticisms, and comments in the following pages that refer to specific sections of the text., which are intended to be constructive and to help improve the quality of the document. This is already a very good document, and my suggestions and comments are intended to help improve it slightly to ensure that it is excellent. Please feel to contact me for any clarifications that you many need. My specific comments follow.

Response: OEHHA thanks Dr. Landolph for his general comments on the "Potential Health Risks of Ethanol in Gasoline" document. All general comments are also addressed in the specific comments, often with greater detail. Responses will therefore be addressed to all to the specific comments.

Specific Comments

Comment 1: Section 2.0 Hazard Identification: Chemicals of Concern. The chemicals of potential concern appear to have been chosen appropriately. Page 3, paragraph 3, line 6: Heptane should also be considered in this analysis, since it is more neurotoxic than hexane, pentane, and octane. "Heptane is considerably toxic to the human nervous system(neurotoxic)." Encyclopedia of Toxicology, Philip S. Wexler, Ed., Volume 2, pages 77-78.

Response: It is assumed that the reviewer is referring to n-heptane, which has a similar chemical structure to n-hexane, a known neurotoxic agent in laboratory animals and humans. n-Heptane is present in the various fuel scenario compositions at levels roughly equal to that of n-hexane. A review of current literature exploring the toxicology of n-heptane in rats did not find any evidence for neurological disturbances at concentrations as high as 3000 ppm for 26 weeks, or 1500 ppm for 30 weeks (Snyder, 1987). Examination of the formation of the neurotoxic metabolites following n-hexane or n-heptane exposure was conducted in both rats and humans (Filser et al., 1996). In both species, urinary excretion of the n-heptane neurotoxic metabolite (2,5-heptanedione) was significantly less compared to the urinary excretion of the n-hexane neurotoxic metabolite (2,5-hexanedione). Also, the neurotoxic potency of the n-heptane metabolite was found to be considerably less than that of the n-hexane metabolite. The authors concluded that for both humans and rats, the neurotoxic potency of n-heptane is significantly lower than that of n-hexane. In addition, two comparative studies observed neurotoxicity in rats following n-hexane exposure, but not following n-heptane exposure

(Frontali et al., 1981; Takeuchi et al., 1980). No human studies on the neurotoxic effects of n-heptane exposure could be located. However, anecdotal evidence in a shoemaker suggests n-heptane may have been involved in the development of peripheral neuropathy (Valentini et al., 1994). However, this case study was confounded by the presence of several other solvents in the workroom air. Based on the lack of evidence for noncancer effects, including neurotoxicity, and the evidence that maximum levels of n-hexane are predicted to be nearly two orders of magnitude below the level of concern, n-heptane was not considered for analysis in this report.

Comment 2: Section 5.1. Estimating Cancer Risk: This section is very well-written and very clearly written. The reviewer suggests a definitive literature citation under section 5. 1, Estimating Cancer Risk, to follow the statement that, "Typically carcinogenesis is treated as a "non-threshold" toxicological phenomenon." Citation of the latest U. S. E.P.A. document on this issue would be helpful here. The reviewer agrees that a non-threshold approach is correct for cancer induction for this section.

Response: OEHHA thanks Dr. Landolph for his comments and agrees that clarification is needed to lead the readers to more information regarding non-threshold carcinogenesis, if they wish to do so. Appendix A contains a detailed toxicity summary of each of the chemicals of concern for this document and includes citations and detailed information on the development of each cancer risk value. A sentence will be added to section 5.0 to direct readers to Appendix A for more information on individual chemicals.

Comment 3: Section 5.1. Estimating Non Cancer Risk: This section is also very well-written and also very clearly written.

Response: OEHHA thanks Dr. Landolph for his comments.

Comment 4: Section 6.1.1: Acetaldehyde: Page 10, para. 2: The authors should take into consideration the sensitivity of asthmatics to acetaldehyde, since asthmatics are likely the sensitive receptors in the population in California, as regards toxicity of acetaldehyde to humans, and since acetaldehyde is very toxic to the pulmonary system.

Response: The acute and chronic Health Protective Values (HPCs) are intended to protect identifiable sensitive individuals, including asthmatics, from harm due to chemical exposure. The application of a 10-fold intraspecies uncertainty factor to the NOAEL is used to account for the known variability within the human population, unless the NOAEL is based on a sensitive subpopulation (i.e. asthmatics) of humans. However, HPCs may not necessarily protect hypersensitive individuals who may develop an idiosyncratic response (including allergic hypersensitivity). Development of the HPCs, including application of uncertainty factors, is contained in Appendix A for each chemical. However, OEHHA agrees this information should be more apparent to the readers of the risk characterization section. Dr. Landolph also expressed similar concern about the irritant effects of ethanol, formaldehyde, MTBE, and PAN in sensitive humans.

Therefore, a sentence will be added to Section 6.1 direct readers to the Appendix for detailed information on the basis and development of the HPCs.

Comment 5: Section 6.1.2. Benzene: Page 19, line 3: The authors should state here, "Acute Myelogenous Leukemia," rather than simply "leukemia," since AML is the type of leukemia that the epidemiological studies definitively indicate is increased in humans upon exposure to benzene.

Response: The sentence “The primary endpoint in human is leukemia.” has been modified to read: “The primary toxic endpoint in humans is acute myelogenous leukemia, but strong evidence exists to suggest that benzene causes other forms of leukemia as well (OEHHA, 1999e).” Also, in response the following sentence has been changed to indicate that the current cancer unit risk value for California is based on total leukemia (i.e., all forms of leukemia as a related class of diseases). (Federal potency values are also based on total leukemia).

Comment 6: The reviewer also suggests citing literature references for induction of AML in humans upon benzene exposure, particularly that from the shoe factory workers in Turkey and other countries. On line 6, the reviewer suggests citing the work of C. Maltoni showing that benzene is a multi-site carcinogen in animals, and also the IARC and U. S. E. P. A. classifications of carcinogenicity for benzene. Page 20, para. 3: Please cite the reference for reduced birth weights in newborns as the most sensitive toxicological end-point for benzene exposure. Also, I suggest indicating that even though this is the most sensitive endpoint, there is no evidence to suggest that this endpoint is of toxicological concern under these scenarios, if this is the case. Otherwise, the sentence is somewhat misleading and tends to imply that there may be a problem with induction of this endpoint under the exposure scenarios, which I do not believe the authors mean to imply. Similarly, in the next sentence, the authors should also cite a literature reference to benzene-induced hematoxicity, including aplastic anemia. They should also state directly that at the exposure levels considered, this is not expected to be a problem, unless they believe otherwise.

Response: OEHHA believes that these comments were adequately discussed in Appendix A, Page A-5. In response to the reviewer’s comments, a reference to Appendix A has been added to “Section 6.1.2 Benzene”. Since there are over 20 epidemiological studies of leukemia among benzene exposure populations as well as numerous animal bioassays, OEHHA has chosen to cite secondary review documents (e.g., ATSDR, 1997; OEHHA, 1999e) to support the points discussed above.

The sentence regarding the noncancer issue will be modified so that it is clear that at the resulting exposure levels, no acute and chronic noncancer effects are expected to occur.

Comment 7: Last two sentences on page 19, and first two sentences on page 20, the reviewer suggests citing the literature on whether benzene carcinogenesis has a threshold, and also citing the official U. S. E. P. A. position on this and the IARC position on this.

Response: Following the sentence describing the threshold issue (first line, page 20), the following citation is added "(reviewed in OEHHA, 1999c)". (Again, a review citation was chosen instead of adding numerous necessary primary citations).

In response to the suggestion for a citation on U.S. EPA and IARC's position on low dose linearity, we have added (after the sentence on line 2 of page 20) the following citations "(OEHHA, 1999c; U.S. EPA, 1999)" to indicate that OEHHA and U.S. EPA treat benzene as a substance that does not function through a threshold mechanism for cancer. IARC does not routinely conduct dose-response evaluations of carcinogens and to our knowledge has not taken a position on the issue.

Comment 8: I suggest adding a few other reference values into the table on cancer slope factors, such as those for strong carcinogens like aflatoxin B 1 and benzo(a)pyrene, and a few weak ones as well, in order to allow the reader to calibrate himself/herself as to the strength of the benzene, butadiene, etc. cancer slope factors, and a small amount of discussion as to how strong the slope factors are for the compounds considered in this document. One or two sentences on this is sufficient).

Response: OEHHA believes that an additional table containing unrelated cancer risk values is not necessary for this document. Table 5c, maximum lifetime cancer risks, and Table 7, lifetime cancer risk and cumulative cancer risks, should allow a more appropriate comparison of cancer risks for the chemicals of concern that will impact the entire South Coast Air Basin.

Comment 9: Section 6.1.3. Butadiene The reviewer suggests citing a literature review on the carcinogenicity of butadiene, on page 20, para 4, line 4. Line 8 should also include a literature reference to the epidemiological studies of butadiene-induced human cancer in epidemiological studies. Many of these comments could be addressed by placing the Appendix section into section 2, if this is consistent with the form this document must take in final form. Similarly, page 21, para. 1, line 1, should also include a reference to the studies of lymphoma induction in mice upon exposure to butadiene. Similarly, lines 5-7 should have a reference or two to the original scientific literature, and also the positions of the IARC and the U. S. E. P. A. on the question of no threshold for this compound should also be mentioned here.

Response: OEHHA thanks Dr. Landolph for pointing out the seemingly disconnect between the listed unit risk values, as well as the noncancer HQs, in the risk characterization section and their basis in the Appendix. Lack of citations for the cancer and noncancer effects for many of the other chemicals are also listed as a concern by Dr. Landolph. As indicated in the previous response, the basis and the development of the unit risk factors and HQs, including a full list of citations, is included in Appendix A. OEHHA believes that for simplicity and ease of reading, the basis and development of

HPCs for individual chemicals should remain separate from the risk characterization. However, this fact will be emphasized in section 6.1 by adding language that will direct the reader to Appendix A for further information on individual chemicals. This should clarify Dr. Landolph's individual concerns regarding citations of critical studies involved in the development of the HPC for each chemical.

Comment 10: Page 21, para. 3, lines 5-7 should indicate that although the most sensitive endpoint for acute exposure is reduced birth weights in newborns and under chronic exposure is ovarian atrophy, there is not expected to be any such induction under the exposure scenarios, if indeed this is the position of OEHHA.

Response: OEHHA agrees that clarification is needed to indicate that the noncancer endpoints will not be reached under the estimated exposure scenarios. Dr. Landolph also expressed a similar concern for the language used in describing the most sensitive noncancer endpoint for some of the other chemicals. OEHHA will modify the discussion of the noncancer endpoints for each chemical, where appropriate, to indicate that under the expected exposure conditions the most sensitive indicator of toxicity will not be reached.

Comment 11: Section 6.1.4. Ethanol, This section is appropriately concise. However, some short discussion regarding the possible effects of ethanol upon the respiratory tracts of the most sensitive receptors, i. e., likely asthmatics, should be briefly mentioned here.

Response: OEHHA thanks Dr. Landolph for his comments. As discussed in a previous response, an intraspecies uncertainty factor is applied to the NOAEL to protect sensitive humans such as asthmatics. Details on the development of the HPC for ethanol can be found in Appendix A.

Comment 12: Section 6.1.5. Formaldehyde, In this section, page 22, para. 2, some mention should be made that formaldehyde and other aldehydes are very irritating and toxic to the respiratory tract. Some concise discussion should be made as to whether levels of formaldehyde would be reached that could be irritating or toxic to the respiratory tracts of humans under the forecast exposure scenarios. On lines 5-7, the original animal studies on the carcinogenicity of formaldehyde to the nasal passages of rats should be cited. Page 23, paragraph 2, lines 4-5 should have a citation to the scientific papers in which these effects were found, and also to data of Henry d'A Heck of CIIT that formaldehyde causes DNA cross-links in cells from nasal passages of rats exposed to formaldehyde. This reviewer is worried about the HQ being 2.4 for formaldehyde at present. This reviewer also agrees that acetaldehyde and other aldehydes likely cause additive effects in terms of respiratory toxicity and ocular toxicity. These respiratory effects could be dangerous in asthmatics, who should be considered the sensitive receptors in the population of humans in California that could be exposed to gasoline. Some modification to the sentences on page 23, para. 2, lines 9 and 10 should

be made. An HQ of 2.4 is too high when the entire population of California would be exposed to acetaldehyde.

Response: OEHHA thanks Dr. Landolph for his comments on the formaldehyde risk characterization. As indicated in section 5.2, the exceedance of an HQ of one does not necessarily mean that a health impact will in fact occur. It is impossible to calculate the lowest concentration at which any one individual in a diverse population would respond. The interpretation of the HQ for formaldehyde currently present in the risk characterization is the most concise analysis that OEHHA can reliably report, given the wide interindividual differences in response and generally limited information. The citations that Dr. Landolph requests can be found in the Appendix A toxicity summary for formaldehyde. However, a sentence will be added to the summary to include the DNA cross-link findings as Dr. Landolph suggests. As discussed in an earlier response, the application of a 10-fold intraspecies uncertainty factor to the NOAEL is used to account for the known variability within the human population, unless the NOAEL is based on a sensitive subpopulation (i.e. asthmatics) of humans. The application of uncertainty factors for individual chemicals can be found in Appendix A. OEHHA thanks Dr. Landolph for revealing that OEHHA did not adequately explain that the annual average exposures for formaldehyde (and the other chemicals) are actually based on South Coast Air Basin (SCAB) scenario estimates. A statement clarifying this point has been added to Section 4.0 of the report.

Comment 13: There is some inconsistency between lines 1-3 and lines 11- 12, in terms of formaldehyde concentrations being two-fold above the REL (lines 1-3) and again being two-fold below the acute REL (lines 11- 12). Please be consistent here.

Response: OEHHA thanks Dr. Landolph for pointing out this apparent inconsistency. As explained in the formaldehyde risk characterization, the proposed chronic REL is currently going under review and may change. If the value for the chronic REL is increased, the disparity between the acute and chronic REL will become smaller. However, animal studies have indicated that near the chronic LOAEL, acute and subchronic exposures to formaldehyde may not result in any microscopic histopathological inflammatory changes to the nasal epithelium. With longer, near lifetime exposures at the same concentrations, inflammatory changes will indeed develop in the nasal cavity. This same sort of scenario may be a contributor to the disparity between the acute and chronic REL.

Comment 14: Section 6.1.6. Methyl t-Butyl Ether(MTBE). Page 24, para. 1, lines 2-4: Please cite the original scientific literature from which these data are derived to strengthen this document.

Response: The citations for MTBE may be found in Appendix A.

Comment 15: Line 10: Please state directly that you are utilizing a linear, no-threshold model for MTBE carcinogenesis.

Response: Upon review of the risk characterization for MTBE, OEHHA agrees that the type of cancer potency model used for unit risk factor development was not clearly stated. Language will be included to show that a non-threshold model was used.

Comment 16: Para. 2, lines 3-5: Why is the 2003 scenario showing a 30% lower cancer risk? Please explain this.

Response: The paragraph in question shows that the 1997 cancer risk from MTBE in MTBE-containing fuel is 3.6 excess cancer cases per million people exposed. The MTBE risk based on 2003 MTBE-containing fuel is shown in parenthesis as 2.5 excess cancer cases (per million people exposed). 2.5 / 3.6 equals a 30% reduction in cancer risk. OEHHA will clarify this paragraph so the 30% reduction in cancer risk is more apparent.

Comment 17: Further, the authors should point out that with a population of thirty million, 3.6 excess cancers per million becomes 102 excess cancers per 30 million. This is getting to be too high an excess cancer risk, in my opinion.

Response: OEHHA thanks Dr. Landolph for revealing that OEHHA did not adequately explain that the annual average exposures for MTBE (and the other chemicals) are actually based on South Coast Air Basin (SCAB) scenario estimates. Dr. Landolph also expressed this same concern regarding the cumulative excess cancer cases as presented in section 6.3. The SCAB is known to have the worst air quality in the State. When Dr. Landolph states “102 excess cancers per 30 million”, he appears to be estimating the excess cancer risk for the entire State of California based on the estimated annual average MTBE exposure in the SCAB. Therefore, using the MTBE cancer risk values for the entire State overestimates the MTBE cancer risk for the population of California. OEHHA will incorporate language into section 4.0 to clarify this misunderstanding.

Comment 18: Page 24, paragraph 3: Please state whether or not these toxicological endpoints would occur in sensitive receptors, i. e., asthmatics, in MTBE-gasoline exposed populations at ambient concentrations. MTBE is a very irritating substance for humans. Scientific studies on the human toxicity of MTBE should also be cited here. What is the projected increased effect of MTBE-containing gasoline upon asthmatics and cigarette smokers in regards to pulmonary toxicity?

Response: As discussed in earlier responses, similar concerns were expressed by Dr. Landolph for other chemicals. Regarding MTBE, as well as the other chemicals, please refer to the Appendix A toxicity summaries.

Comment 19: Section 6.1.7. Peroxyacetyl Nitrate (PAN). Page 25, para. 2: The authors should cite the scientific papers dealing with the toxicity of PAN, particularly review articles. Secondly, these acute noncancer HQ values for PAN at 2.4 are too high.

Page 25, last sentence, and 26, top line: Do the authors feel that any of these endpoints may at any time be induced in humans being exposed to PAN in ambient air due to PAN in gasoline? Please state this one way or the other definitively, or indicate the uncertainty.

Response: Citations for PAN are located in Appendix A. OEHHA acknowledges that the potential for sensory irritation from PAN, as explained in the document, was somewhat vague. To rectify this problem, OEHHA will incorporate language similar to that found in section 6.1.5. (formaldehyde): "It is possible that some sensitive individuals may develop acute adverse effects at the maximal predicted exposure. Simultaneous exposure to other sensory irritants, such as formaldehyde, may exacerbate the eye irritation caused by PAN".

Comment 20: Re Table 5a: This reviewer is concerned about the HQ values for formaldehyde and PAN. Please give us HQ values for all the other HQ's added together, and also lifetime cancer risk values when all the lifetime cancer risk values for each compound are added together. This reviewer is concerned about the cumulative, additive HQ values for formaldehyde, PAN, and the other values added together for sensitive receptors, i. e., asthmatics. Please comment on this.

Response: Tables addressing the combining of HQs, known as Hazard Indexes (HIs), can be found in section 6.4, Cumulative Noncancer Impact of Multiple Chemical Exposures. This section also discusses how to interpret these results, and their limitations. Tables that address the combining of lifetime cancer risk values can be found in section 6.3, Cumulative Cancer Impact of Multiple Chemical Exposures.

Comment 21: It is also noteworthy that the benzene cancer risks decrease under the 2% ethanol/2003 and the 2003 NonOxy/2003 scenarios compared to the 1997 values. Similarly, the formaldehyde cancer risks decrease from the 1997 values under all four 2003 scenarios. This seems to indicate that eliminating MTBE would eliminate MTBE pollution and its carcinogenicity and toxicity, without significantly altering the concentrations of the other toxic and carcinogenic pollutants. This is good. However, the cumulative HI and lifetime cancer risk values may still be too high to adequately protect public health. More thought needs to be given to this issue.

Response: OEHHA agrees that the lifetime cancer risk and some cumulative HIs appear to be excessive. However, OEHHA noted in the report that for both the individual chemicals and their cumulative effects, there are numerous uncertainties to take into account when interpreting these numbers. Given this, it is the risk managers for the air management districts (e.g., the South Coast Air Quality Management District) and CARB that would use the hazard estimates determined by OEHHA and decide if appropriate measures are be taken to protect public health.

Comment 22: Section 6.2. Risk Characterization for Other Compounds of Concern: - Page 29, paragraph 1: The authors should give a one paragraph, concise discussion on the

toxicity and carcinogenicity of toluene, xylenes, isobutene, and n-hexane, particularly with regard to their neurotoxicity to humans.

Response: The potential for carcinogenicity and toxicity for each of the chemicals listed above is summarized in Appendix A. OEHHA will include a sentence in section 6.2, Risk Characterization for Other Compounds of Concern: Toluene, Xylenes, Isobutene, n-Hexane to inform readers of the presence of these summaries in the Appendix.

Comment 23: The reviewer suggests mentioning that although there are large uncertainty values associated with lifetime cancer prediction, nevertheless, there is firstly good news that all aggregate lifetime cancer risk values are lower in 2003 than in 1997, and secondly, that the 2% ethanol and 3.5% ethanol formulations are the lowest among these, and decrease from 290 to 190, which is a 34% decrease of the upper values, and from 270 to 170, which is a 37% decrease in the lower bound values. This is very good news, and it should be emphasized. It suggests that the State of California may be able to eliminate the MTBE in the gasoline, and get even lower lifetime cancer risks for its population, plus eliminate the problem of MTBE from leaking gasoline storage tanks fouling the water supplies from wells.

Response: OEHHA agrees that the reduction of cancer risk under the 2003 scenarios compared to the 1997 fuel scenario is an encouraging result. However, we feel it is important to maintain a technical presentation of the results. As discussed in our report, given the uncertainties in the individual chemical estimates and the inherent uncertainty in addition of multiple cancer risk estimates, OEHHA believes the differences in cumulative cancer risk between the four 2003 formulations are not significant.

Comment 24: Another consideration that should be mentioned is that even at a lifetime cancer risk of 170/million(2003 lower bound scenarios), this would translate to 170 x 30 or 5, 100. extra cancers in the State of California due to the carcinogens in gasoline. OEHHA should consider recommending to the Governor of California that California move slowly and gradually away from gasoline-powered vehicles(to minimize economic disruption) and continue to move toward solar-powered vehicles, electric-powered vehicles, and more public transportation. These calculations are very illuminating. It should also be stated that any change in gasoline formulation is an experiment on the people of California. It should be done very carefully, perhaps in one part of the State at a time, to ensure we are not causing any harm by this change in gasoline formulation. It appears from the data in this table 8 that if the State of California shifted from MTBE-containing gasoline to 2% or 3.5% ethanol-containing gasoline, that the HQ value would be similar to or the same as that for MTBE gasoline, and one could eliminate the water-fouling, toxic, and carcinogenic properties of MTBE that arise when gasoline tanks leak MTBE-containing gasoline. However, these HI values are still too high, and again it should be pointed out that a gradual shift away from gasoline-powered vehicles and toward solar-powered and/or electric-powered vehicles, and also toward more use of public transportation should be serious goals for California in the future.

Response: OEHHA shares Dr. Landolph's concern that the cumulative cancer risks and HI's presented in our report may indeed result in important public health issues, particularly for the people living in the South Coast Air Basin where these emission estimates were modeled. OEHHA's current mandate with regard to the ethanol fuel report is to present Californians with the cancer and noncancer risks scenarios associated with the various fuel formulations. It is conceivable that OEHHA will be asked in the future to develop airborne hazard risk estimates based on alternative transportation means and alternative fuel vehicles. However, it is primarily the purview of the California Air Resources Board (CARB) to address these issues. OEHHA will strive to present to the public the most up-to-date health hazard assessments associated with fuel combustion emissions.

Comment 25: Section 6.4. Cumulative Noncancer Impact of Multiple Chemical Exposure**.** This section is written well and in a clear fashion. At the end of paragraph 3, page 34, the authors should discuss that the cumulative (added) HI values firstly are considerably in excess of 1.0, and in fact are as high as 6.9(1997 MTBE value). It seems to this reviewer that this is simply too high a cumulative HI value. This should be discussed in terms of its impact on human health. All attempts should be made to lower this value. It appears from the data in this table 8 that if the State of California shifted from MTBE-containing gasoline to 2% or 3.5% ethanol-containing gasoline, that the HQ value would be similar to or the same as that for MTBE gasoline, and one could eliminate the water-fouling, toxic, and carcinogenic properties of MTBE that arise when gasoline tanks leak MTBE-containing gasoline. However, these HI values are still too high, and again it should be pointed out that a gradual shift away from gasoline-powered vehicles and toward solar-powered and/or electric-powered vehicles, and also toward more use of public transportation should be serious goals for California in the future.

Response: OEHHA thanks Dr. Landolph for his comments. With regard to the cumulative HI values, as indicated in section 5.2, the exceedance of an HQ (or an HI) of one does not necessarily mean that a health impact will in fact occur. It is impossible to calculate the lowest concentration at which any one individual in a diverse population would respond. The interpretation of the cumulative HIs is the best analysis that OEHHA can reliably report, given the wide interindividual differences in response, the generally limited information, and the uncertainties that go into combining HQs for a given endpoint. With regard to encouraging the public to use alternative methods of transportation, OEHHA's mandate is to present Californians with the cancer and noncancer risks assessments associated with the various fuel formulations. It is conceivable that OEHHA will be asked in the future to develop airborne hazard risk estimates based on alternative transportation means and alternative fuel vehicles. However, it is primarily the purview of the California Air Resources Board (CARB) to address these issues.

Comment 26: In addition, for Table 9, regarding respiratory toxicity, this reviewer was again surprised that the HI values were as high as 3.9 - 4.0 for the 1997 MTBE-containing gasolines. It is gratifying that no matter which of the four formulations

of gasoline is used in 2003, the HI values decrease to as low as 3.7(upper bound) or 3.6 (lower bound), which represent decreases of 7.5% and 7.7%, respectively. This is very good news, and it should be stated this bluntly in this section and is cause for optimism. It should also be stated that it looks like the State of California can move to 2% ethanol-containing or 3.5% ethanol-containing gasoline, not cause any significant increase in respiratory HI values, and eliminate any further increases in the MTBE pollution of the water sources in California due to leaking underground storage tanks. This should be stated precisely in the discussion to this section. Similar statements apply to Tables 9 and 10, and these statements should be made more boldly in the discussion of these two tables.

Response: OEHHA shares Dr. Landolph's optimism concerning the reduction in HI values resulting with the 2003 fuel scenarios. However, given the limitations in the estimates, as described in section 6.4, the reductions in HI values can be considered only modest at best. Also, it should be emphasized that these reductions, according to CARB's companion document to this report, result from an overall reduction in fuel emissions. All in all, OEHHA agrees that including additional statements emphasizing the modest reductions in HI values will enhance the interpretation of the noncancer results. OEHHA believes that MTBE's air quality impact is relatively small in comparison to its impact on water quality. The greatest impact of removing MTBE from gasoline is detailed in section 6.5, Health Impacts of Drinking Water Contamination by Gasoline Components.

Comment 27: Page 35, para. 2, lines 3-5: What the authors say is factually correct. However, the reviewer is more worried about the HI for these two substances exceeding 1.0 individually, and that the cumulative HI is as high as 5 for table 10. This should be mentioned more strongly.

Response: OEHHA thanks Dr. Landolph for his comment. A sentence will be added to the paragraph to emphasize that, individually, these substances (formaldehyde and PM10) may result in chronic respiratory irritation in sensitive people.

Comment 28: Page 38, para. 3, lines 2-3: Values for tertiary butyl alcohol are not listed in Table 4. Please list them or correct this sentence.

Response: OEHHA thanks Dr. Landolph for alerting OEHHA to an error in this paragraph. The correct table referring to the health protective concentrations for drinking water is actually Table 3, not Table 4 as indicated. The CARB could not detect measurable air levels of tertiary butyl alcohol in the South Coast Air Basin. Therefore, it is not listed in Table 4.

Comment 29: Page 38, para. 4, line 5: "organoleptic" is a sophisticated but not a commonly used scientific word. Please substitute another word, such as toxic and/or noxious. Also, in this paragraph, please reference the appendix or the original scientific literature on the toxicity and carcinogenicity of MTBE.

Response: OEHHA agrees that "organoleptic" is not a commonly used word in general toxicology circles. However, its use is much more common in reference to water pollution issues and is appropriate in the discussion of drinking water contamination by gasoline components. OEHHA will include, in parentheses, the one word definition (i.e. noxious) provided by Dr. Landolph.

Comment 30: Section 6.5. Health Impacts of Drinking Water Contamination by Gasoline Components: This section is very well-written, and it suggests that ethanol contamination of the water due to use of ethanol in gasoline should present very minimal toxic and carcinogenic risk and no objectionable taste or smell problems for public drinking water. A concluding sentence such as this should be placed at the end of this section to wrap this section up well. The fact that ethanol is biodegraded rapidly is also cause for cautious optimism. However, the reviewer recommends being cautious in the area of ethanol, since there is little or no data on the pulmonary effects of ethanol or ethanol-containing gasoline.

Response: OEHHA agrees that a concluding statement as offered by Dr. Landolph will enhance the interpretation of the water contamination issues and will be added to section 6.5.

Comment 31: Section 6.6.2. Uncertainties in Exposure Assessment, Page 43, para. 3: The authors should indicate some of the data that went into the assessment of lesser gasoline use in 2003 compared to 1997, particularly since the number of people living in the State of California is increasing dramatically with time.

Response: OEHHA agrees that the primary reasons for the year 2003 reduction in emissions are not clearly explained. OEHHA will add a sentence to Section 6.6.2 to clarify that the ARB assumptions of reduced air emissions for 2003 are based on a total reduction of overall fuel emissions. It is expected that at least a portion of these emission reductions will result from an increased proportion of cleaner fuel-burning, vehicles on California roads.

Comment 32: This report could also use an Executive Summary of no more than 250 words at the front.

Response: OEHHA agrees that an executive summary would enhance the document. One is being prepared that will include the analysis by OEHHA, as well as the analysis of the California Air Resources Board and the State Water Resources Control Board.

Comment 33: Section 7.0. Research Needs, This section is appropriately written, but is somewhat dry. The authors should add some more enthusiasm to this section, since it will be widely read. In particular, this section should emphasize the need for more research on the pulmonary toxicity of ethanol alone and of ethanol-containing gasoline.

Response: While this section may be somewhat dry, it should be stressed that this section is a work-in-progress and will be modified in future drafts. OEHHA will modify this section to include Dr. Landolph's timely comments on the need for research on the pulmonary toxicity of ethanol and ethanol-containing gasoline.

Comment 34: Section 8.0 Summary/Conclusions.- On page 52, either at the end of para. 1, or as a separate para., I recommend inserting: "Further efforts to encourage Californians to utilize electric-powered cars or solar-powered cars, or public transportation, to reduce the cumulative HI values even farther, and preferably to 1.0 or below, should be made. This is particularly important to protect the health of sensitive receptors, such as asthmatics, athletes, and children."

Response: OEHHA commends Dr. Landolph on his encouragement of Californians to use cleaner transportation options. However, it is not the mandate of OEHHA to begin a conversation about other fuel alternatives in this document. Laying out the airborne health risks associated with the various fuel scenarios will generate such discussion.

Comment 35: Appendix A: Toxicity Summaries: This section is excellent. The authors should make better use of it, by stating in the earlier sections, "summarized in the Appendix." This would also strengthen the earlier sections.

Response: This helpful comment was addressed in an earlier response. The statement "summarized in the Appendix" or similar language will be included in the main document where appropriate.

Comment 36: Editorial Comment: This reviewer really likes the comprehensive reviews of the toxicity of the various gasoline components in the Appendix. This reviewer recommends that the Appendix be placed at the front of the report, on page 2, Chemicals of Potential Concern. It helps a scientist understand how these COPC were identified, and to appreciate the toxic and carcinogenic risks that these substances can pose in the air.

Response: OEHHA appreciates Dr. Landolph's comment. However, for the sake of simplicity and ease of reading by a general audience, the toxicity summaries in Appendix A will be kept out in the main body of the text.

Comment 37: The country of Brazil has used ethanol as a fuel in automobiles for many years. Some attempts should be made to capture in this document the health effects if any in humans that use of ethanol as a fuel has caused. The Brazilian experience, if it has been documented, would be invaluable to capture for California in this document before any final decisions on gasoline reformulations are made.

Response: OEHHA thanks Dr. Landolph for highlighting the presence of these data in the literature. In fact, the CARB cites this Brazilian study in the companion document to this report. As part of their evaluation of the potential air quality impacts of

substituting ethanol-blended gasoline for MTBE-blended gasoline, the Air Resources Board conducted a literature review of related programs implemented elsewhere. The studies of the impact of the use of ethanol fuel on air quality conducted in Denver, Albuquerque, and Brazil provided the most useful insights.

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B.1.2. Comments of Dr. Greenberg

Peer review comments on the document "Potential Health Risks of Ethanol in Gasoline" were received from Dr. Alvin Greenberg.

General Comments

Comment 1: Any risk assessment is usually written for a specific audience. For this document, it is unclear who the intended reader is and the level of scientific sophistication of that reader. As a result, I found some sections to be very remedial in nature while others were in need of additional explanation and/or clarification.

Response: Thank you for the comment. The body of the text is intended for a more general audience, as opposed to the appendix which is intended to provide a more detailed scientific description of chemical toxicity. OEHHA staff will work to make the language in body of the text more consistent for a general audience.

Comment 2: The document also lacks an Executive Summary with accompanying summary tables, a tool I have found very useful in risk communication. As I read the document, I found myself constructing such a table from the information presented in various sections. This table could prove very useful in describing in "pictorial" format (as opposed to narrative format) the overall conclusion of the document. Thus, I suggest the inclusion of a brief Executive Summary with a table which depicts each chemical assessed, the unit risk value and noncancer REL (or appropriate health-protective Level), the degree of 'uncertainty about that value in relative terms (high degree of uncertainty, medium, low and very low), and the net effect on ambient levels in three future scenarios (2% EtOH, 3.5% EtOH, and non-oxy fuel) as compared to the present scenario (1997 w/MTBE) and expressed as decreased levels, slightly decreased levels, slightly increased, increased, or little change (remains about the same). The final line of this table could represent the cumulative impacts showing a slight decrease in risks and hazards.

Response: OEHHA agrees that an executive summary would enhance the document. Thank you for your specific suggestions regarding a table. An executive summary is currently being compiled that will include the analyses of OEHHA, the California Air Resources Board (CARB) and the State Water Resources Control Board (SWRCB). OEHHA will incorporate an overall health assessment table in the executive summary that will present the total picture of the air impact of the ethanol fuel alternatives.

Comment 3: I was pleased to find a section on research needs in this document. I found the tables in §7 to be most informative. The toxicity profiles found in Appendix A are particularly well written and consistent.

Response: Thank you for the comment.

Specific Comments:

Comment 4: §2.0 Hazard Identification: Chemicals of Concern. It is unclear from reading this section and section 4.0 Exposure Assessment how (and even if) *"the impacts from evaporative emissions, exhaust emissions, as well as secondary transformation products"* were assessed in this document. I understand that CARB provided the modeling for these three emissions sources but §4 lacks even the mention of these sources. A brief qualitative description of the modeling results (perhaps describing the relative contribution of each to airborne levels) would be helpful.

Response: OEHHA thanks Dr. Greenberg for his comment. OEHHA has added the following language to section 4 to clarify the sources of emissions modeled by CARB:

"The CARB conducted modeling analyses of the air quality impacts of use of one fuel versus another. The South Coast airshed was selected as the basis of their modeling efforts since the South Coast is a severely impacted area of the State and one which has been extensively studied. The CARB analysis includes consideration of the changes in ambient air concentrations of specific toxic components of exhaust, evaporative components, and subsequent reaction products that would result from substituting ethanol-blended gasoline for gasoline blended with MTBE. The modeled air concentrations incorporate all sources of emissions within the South Coast airshed, including stationary source emissions, mobile source emissions and background emissions. However, stationary source and background emissions are not expected to change between the various fuel scenarios…"

We feel this adequately summarizes CARB's work. Readers are referred to CARB's document for further details.

Comment 5: It is also unclear how the *"chemicals determined to be the most important in terms of public health risk"* were selected. Was this an "intuitive" process or a more formal process using screening information or toxicity scores. I don't disagree with the chemicals selected; I feel that the document should be clear in the process and identify any chemical which was initially considered but dropped from the list for whatever reason. This becomes an important issue when reading §6.6 (see below).

Response: The selection relied on identification of fuel constituents and atmospheric products by CARB, and initial screening of available toxicological data. An informal process was used. The document will be amended as follows (Sec 2, para 2.):

"CARB provided the speciation profiles for the air emissions and modeling to determine concentrations of key chemicals from the four fuels. OEHHA focused this analysis on key chemicals associated with fuel use and potential changes in air concentration of those chemicals. Selection of chemicals of concern initially relied on the identification of representative fuel constituents and atmospheric contaminants by CARB, and a preliminary assessment of toxicological data available from secondary sources in the literature. The chemicals determined to be the most important in terms of public health risks, which were selected for more detailed evaluation for this report, are: ... "

Comment 6: §3.1.1 Carcinogenic Endpoints. The document states that the unit risk values are *"usually a 95% upper confidence limit of the slope of the dose-response curve"*. If values other than the 95% UCL were used, they should be identified. If none, than drop the term "usually" for this report.

Response: For clarification, the word 'usually' has been dropped. OEHHA intended to indicate that not all unit risk or cancer potency factors that have been developed by other U.S. agencies used the 95% upper confidence limit in representing the upper bound estimate of the risk. However, with regards to the chemicals presented in this document that have unit risk factors or cancer potency factors, all were calculated with a 95% upper confidence limit of the slope of the dose-response curve, representing an upper bound estimate of the risk.

Comment 7: §3 Table 3. Health Assessment Values. Ethanol is considered to be non-carcinogenic in this document. Yet, the human data show increased incidence of esophageal cancer in persons who drink and smoke heavily. This fact should be discussed and either dismissed as a "high-end dose" effect or included and assessed.

Response: Thank you for the suggestion. OEHHA is adding language to the ethanol summary in Appendix A to reflect this comment, as well as suggestions from other commenters.

Comment 8: § 4 Exposure Assessment. Table 4. The health effects tables in §3 list the relevant health levels in both ppb and the more appropriate $\mu g/m^3$. Table 4 lists predicted airborne concentrations in ppb only. Please add the values in $\mu g/m^3$.

Response: OEHHA thanks Dr. Greenberg for his suggestion that presenting the values in $\mu g/m^3$ would be more appropriate. However, OEHHA believes that for the purpose of consistency, the values in Table 4 should be presented in the same units as that provided by CARB. OEHHA also feels that units expressed as ppm or ppb is more suitable for a general audience. OEHHA does agree with Dr. Greenberg that $\mu g/m^3$ is a more appropriate scientific notation and is therefore used in the toxicity summaries, in addition to the ppm or ppb notation in the Appendix.

Comment 9: It is my understanding that the 1997 MTBE, the 2003 MTBE, and the 2003 Non-Oxy scenarios lack ethanol in the fuel supply. Why then is an airborne concentration for ethanol listed for these three scenarios? MTBE is listed as "zero" for the three "no MTBE" scenarios. Shouldn't it be the same for the three "no Ethanol" scenarios? Please explain.

Response: OEHHA thanks Dr. Greenberg for pointing out this apparent inconsistency. In CARB's report, other sources of emissions, including stationary sources, were included in the emission analysis. Therefore, CARB's predicted atmospheric concentrations for the South Coast Air Basin as presented in Table 4

represents all sources of atmospheric emissions, including both mobile and stationary sources. The ethanol emissions shown in the non-ethanol-containing fuel scenarios are primarily from stationary sources, such as consumer products. There are no detectable MTBE levels in the atmosphere under non-MTBE-containing fuel scenarios because stationary sources of MTBE are negligible. OEHHA will incorporate language in section 4 to clarify this issue.

Comment 10: § 6.1.6 Risk Characterization of MTBE. The document states that, *"In the 2003 scenario with the same MTBE-containing fuel, the predicted concentration of MTBE in air … is approximately 30% lower."* This statement is supported by the modeling results found in Table 4 yet there is no explanation for this finding in this section. This decrease is shown for all chemicals of concern and again, no explanation is provided. Perhaps the explanation resides in §6.3, page 32, where the reduction is explained as being due to "expected reductions in overall emissions". Or, perhaps the explanation resides in the CARB report on modeling but it would be useful to provide one here. The fact that this document estimates a decreased risk in the year 2003 under the "do nothing" scenario might be cause for scrutiny.

Response: OEHHA thanks Dr. Greenberg for pointing out the vagueness of this statement. OEHHA intended to simply state that the estimated cancer risk for MTBE is reduced by 30% under the 2003 scenario, as compared to the 1997 scenario. The paragraph in question shows that the 1997 cancer risk from MTBE in MTBE-containing fuel is 3.6 excess cancer cases per million people exposed. The MTBE risk based on 2003 MTBE-containing fuel is shown in parenthesis as 2.5 excess cancer cases (per million people exposed). 2.5 / 3.6 equals a 30% reduction in cancer risk. OEHHA will clarify this paragraph so the 30% reduction in cancer risk is more apparent.

Comment 11: §6.3 Cumulative Risk. The discussion on page 33 regarding a potential for increased exposure and risk in areas located near freeways or fuel depots warrants further assessment. While I realize that this is not an easy task, CARB is developing and using models to address a similar scenario as part of the risk characterization of diesel exhaust. Because the document readily admits that the risk assessment results were dependent upon *"population-weighted annual averages* a typical exposure along a freeway may very well be underestimated. And while it is true that this assessment is undoubtedly more precise in describing the relative differences between the different fuel scenarios, some of these differences now identified as small (or insignificant) may in fact be larger for a more heavily exposed populations. Further assessment is needed to answer that question.

Response: OEHHA agrees that further exposure assessment is needed to fully answer this question, and that this information would enhance the document. CARB is continuing to study various exposure scenarios. As more exposure data specifically addressing “hot spots” (e.g. exposures near freeway and fuel depots) become available from CARB, this report will be updated to reflect any possible new findings and conclusions.

Comment 12: §6.4 Cumulative Noncancer Impact of Multiple Chemical Exposures.

While it is clear that document seeks to assess the relative differences in risk/hazard posed by the various fuels and does not lay claim to present absolute risks/hazards of each formulation with great accuracy, the reader of this document will nevertheless focus some attention on the absolute risk/hazard of each fuel. This may be particularly true when it comes to the review and evaluation of the hazard index due to the release of respiratory irritants, including the criteria pollutants. Therefore, it may be useful to include background levels of the criteria pollutants in the South Coast Air Basin, an act consistent with the AB2588 risk assessment guidelines. This could be presented in a separate table distinct from Tables 9 and 10 and with a suitable narrative description.

Response: The exposure estimates for 1997 and 2003-MTBE fuel scenarios include background levels, as well as all stationary sources, of the criteria pollutants. OEHHA believes that presenting background levels of the criteria pollutants in the South Coast Air Basin would not provide a useful purpose to the intended audience and may detract from the focus of the report (i.e. differences in overall airborne levels of pollutants under various fuel alternatives).

Comment 13: §6.6 Uncertainties and Data Gaps. Other chemicals of concern are discussed in section 6.6.1. It appears that many of these chemicals, although emitted or formed as a result of atmospheric transformation, were not included in the risk assessment due to lack of suitable toxicological data. It is my view that all potential chemicals of interest should be listed in sections 2 and 6 along with all known and relevant toxicological data. If it is then determined that they would not influence the risk assessment significantly, they could be removed from consideration. For some, surrogates could be used and hence an "upper-bound" of risk and hazard could be calculated. A summary of this effort could be depicted in tabular form.

Response: OEHHA prefers to limit the chemicals listed in section 2 to those included in the quantitative analysis. OEHHA believes this will provide a more concise and straightforward presentation of those chemicals of concern. We were unable to find any useful data on the other chemicals of concern discussed in section 6.6.1 to estimate their potential public health risk. We prefer to leave those chemicals for discussions of uncertainty, data gaps, and research needs.

B.1.3. Comments of Dr. VandeVoort

Peer review comments on the document “Potential Health Risks of Ethanol in Gasoline” were received from Dr. VandeVoort (University of California at Davis).

General Comments

Comment 1: This report carefully details the source of data that was used to calculate risk assessment of potential health impacts for four options of future fuel composition.

The report also emphasizes that because most of the available data in the literature is based on exposure to one chemical at a time, and that gasoline is a complex mixture of

chemicals and subsequently reacted or partially-reacted compounds, that the conclusions of the relative risks from gasoline exposure are probably inaccurate.

Response: OEHHA would like to clarify that we do not consider the relative risks from the gasoline fuel scenarios as 'probably inaccurate'. Rather, one of the primary conclusions that OEHHA established from the risk analysis is that there is more confidence in the relative differences between fuels than the absolute magnitude of the risk faced by the exposed population under the various scenarios considered. Comparison of the aggregate cancer and noncancer risks among the five fuel scenarios gives a reasonably good indicator of the relative impact of each fuel on the cancer and noncancer risk from airborne pollutants in the South Coast Air Basin.

Comment 2: The appendix A summarizes the various toxicities of the chemicals found in gasoline or their transformed by-products. These summaries appear to be accurate, but of course these statements are only as complete as current research in the literature. I happen to feel strongly that the mouse and rat are not adequate models for the studies of human female reproductive and developmental effects of these compounds. Tables 11 and 12 carefully detail where the need for further research is the greatest and the report clearly states how this lack of information can affect the accuracy of the predicted potential health effects of the four fuel options.

Response: OEHHA thanks Dr. VandeVoort for her general comments on the "Potential Health Risks of Ethanol in Gasoline" document. OEHHA has been careful to identify uncertainties and data gaps in the information presently available, and is undertaking further risk assessment of fuel-related pollutants, particularly in response to new data as these become available.

Major Points of Concern:

Comment 3: Although ethanol is a common dietary component for many people, it is not without risk. As this report states, there is little information available on the risk of inhaled ethanol. Also, ethanol is both water and fat soluble and can be used to emulsify or solubilize many compounds that would otherwise be water insoluble. Therefore, care must be taken in evaluating the long-term effects because of the potential of ethanol to change the interaction of chemical mixtures.

Response: OEHHA agrees that research is needed to investigate the potential of ethanol to change the interaction of chemical mixtures. As stated in section 6.5, research is currently being conducted to determine whether any secondary effects of ethanol, such as enhancement of migration through soil, or acceleration or inhibition of biodegradation, would alter the concentrations of compounds of concern (such as benzene) in impacted wells. Preliminary screening model results by the Lawrence Livermore National Laboratory indicate that the cosolvency effect of ethanol is not likely to play a significant role in influencing groundwater transport of benzene. It is expected that the cosolvency effect of ethanol will be at least partially offset by the rapid biodegradation of ethanol in soil, particularly in comparison to MTBE.

Comment 4: One major omission from the report is any evidence that an attempt was made to get data from the midwest where gasohol (gasoline with ethanol) has been in use for decades.

Response: Dr. VanderVoort's concern is addressed in the California Air Resources Boards' (CARB) companion document to this report. The CARB presents the results of a literature review conducted to find studies that measure the direct impact of the use of ethanol in gasoline on air pollution. All these studies addressed the effects on atmospheric concentrations of compounds of concern: direct, systematic comparisons of health effects in comparable areas using fuels with and without ethanol do not appear to have been undertaken. Two of the three most useful studies identified by the CARB were conducted in Denver and Albuquerque.

Comment 5: One of the major problems with this report is that the atmospheric concentration estimates are not derived by the OEHHA, but rather are furnished by the CARB, and therefore there is no explanation of how the levels of chemicals are rationalized. An example of this is formaldehyde. Table 4 presents the CARB data on atmospheric concentrations of pollutant levels for various scenarios. Formaldehyde levels are the same regardless of scenario. Although MTBE is transformed into formaldehyde and ethanol is not, the levels of atmospheric formaldehyde are equivalent. This would seem to defy common sense. Another problem with the CARB data is which chemicals were included and which were not. Atmospheric levels of xylenes are not included, despite the fact that they are included in Appendix 1 and they are identified as having adverse health effects. Other chemicals not included are listed on page 29.

Response: The predicted change in air concentrations of pollutants due to the use of ethanol-based fuels is discussed in the CARB's companion document to this report. In brief, CARB used the best available information on the emission characteristics of fuels that will be available in 2003, along with a comprehensive analysis of current air quality concentrations and a state-of-the-science photochemical model to estimate air quality in the future under the various fuel scenarios. The final report delivered to the Environmental Policy Council will include the full reports from OEHHA, CARB and SWRCB, and also an Executive Summary which OEHHA believes will make the relationship between the different phases of the risk assessment process clear.

CARB estimates that for all three MTBE-free gasolines, there will only be a modest overall reduction of 2 to 4% for formaldehyde compared to the 2003 MTBE-fuel gasoline (as reflected in Table 4). The formaldehyde emissions resulting from the combustion of the non-oxygenated fuel components is partly the reason for this modest reduction in formaldehyde. However, the atmospheric concentration estimates presented in Table 4 also include total emissions (mobile, area, stationary, and natural sources) of formaldehyde in the South Coast Air Basin. Thus, the reductions in formaldehyde due to use of ethanol-based fuels are 'diluted' when all primary and secondary sources of formaldehyde are included. Because Dr. VandeVoort and other reviewers had somewhat similar concerns about Table 4 and section 4, OEHHA has incorporated language to

section 4 to emphasize that our risk analysis is based on total emissions of chemicals of concern in the South Coast Air Basin.

OEHHA thanks Dr. VandeVoort, as well as other reviewers, for concern about OEHHA's decision-making process for chemicals of concern. OEHHA has incorporated language into section 2 to define how a chemical of concern was chosen. As stated in Section 6.2, xylenes were not regarded as a chemical of concern because xylenes are not a suspected human carcinogen and the annual average concentrations found or estimated were substantially below health protective concentration. Therefore, detailed atmospheric levels for xylenes are not presented in Table 4. Nonetheless, a risk characterization for xylenes and some other compounds not considered chemicals of concern are included in Section 6.2 because they are substantial fuel components.

Comment 6: The report states that the evaluation focuses on the key differences resulting from the use of four different fuels (page 43). It is difficult to determine what these key differences are. In fact, the report itself, in the summary/conclusions states "It appears that there are no substantial differences in the public heath impacts of the different non-MTBE fuel formulations considered in the scenarios for year 2003." At this point, someone must be asking why there is a proposal to add ethanol to gasoline when the outcome appears to be the same as that for the non-oxygenated fuel in 2003? Why consider taking an action which may increase risk to public health due to unknown effects of ethanol in chemical mixtures when there appears to be no gain?

Response: This comment is also addressed in CARB's part of the ethanol fuels report. Currently, federal law requires gasoline to include an oxygenate for regions in California designated as non-attainment areas. Under an MTBE ban, ethanol would be the only possible oxygenate. The California Energy Commission anticipates that alkylates will be used in non-oxygenated gasoline and some ethanol-containing gasolines in California to replace the octane normally provided by MTBE. In the event that the federal law for oxygenates is partially or fully rescinded, use of the non-oxygenate fuel may increase in California. However, there is arguably a greater lack of health effects data for some of the alkylates in the non-oxygenated fuel compared to ethanol. The need for more health effects data on the alkylates is noted in section 6.6, Uncertainties and Data Gaps, and section 6.7, Research Needs.

The summary statement quoted refers to the health impacts of air pollution changes expected due to the replacement of MTBE with ethanol as the oxygenate in gasoline. The replacement of MTBE by ethanol was initiated because of the expectation that it would result in substantial water quality improvements. A key requirement of the Executive Order was to determine that the substitution (proposed to improve water quality) would not result in worse public health risks from air pollution. OEHHA considers that the present report addresses this requirement, within the limitations of the data available.

Comment 7: The report mentions in several places that data is not available, such as data on the toxicity of alkylates (page 42). It also states that the report focuses on the

key primary and secondary pollutants, but there is a possibility that a significant chemical has been omitted (page 43). Further confusion arises on page 38 where it is stated that Table 4 shows the health protective concentrations for drinking water for various gasoline components, however Table 4 is the atmospheric concentration data. I found this data in Table 3, however, TBA was not included (as stated in same paragraph). However, there appears to be no data available on what the actual levels of these compounds are in drinking water. Also in the same paragraph, TBA is identified as one of the breakdown products of MTBE. However, it is not listed as one of the "key" pollutants on any of the tables. TBA is known to have adverse effects in male rats (just one example, Acharya et al., Exp Toxicol Pathol 1997 Dec; 49(5):369-73). These statements do not leave the reader with a high degree of confidence in the list of chemicals which have been selected as key chemicals and emphasize the possibility of the omission of something important.

Response: The lack of toxicity data for some alkylates and the possibility that a significant chemical has been omitted are included in the uncertainties and data gaps listed in Section 6.6. As with any risk assessment, some uncertainties and assumptions exist when developing health protective values. This process becomes increasingly challenging when evaluating health risks involving complex mixtures (such as the fuel scenarios) for an entire air basin. OEHHA would be remiss if all the uncertainties, however minor, resulting from these fuel scenarios were not included in the risk assessment. The inclusion of uncertainties is meant to encourage scientific debate concerning the degree of confidence in a health protective value. Just as important, risk assessment is a dynamic process undergoing constant refinement as more toxicity and exposure data is generated. OEHHA and CARB have ongoing research programs to address data gaps, and to evaluate new data as they become available. Laying out the uncertainties and data gaps in a risk assessment is meant to encourage research to increase the degree of confidence in a health protective value and minimize the uncertainties and data gaps.

OEHHA thanks Dr. VandeVoort and other reviewers for alerting OEHHA to the incorrect Table reference in the draft version of Section 6.5. The correct table reference (Table 3) will be inserted in the final version. Tertiary butyl alcohol (TBA) is not listed in Table 4 because the CARB could not detect measurable air levels of TBA in the South Coast Air Basin. OEHHA will also remove the erroneous sentence that indicates health protective values for formaldehyde and TBA are found in Table 3. Regarding the lack of actual levels of key compounds in drinking water, the State Water Resources Control Board did not supply OEHHA with chemical exposure data that would allow quantitative risk estimates for drinking water.

Comment 8: Another unknown factor is what compound will be used to denature the ethanol. Denaturation of the ethanol is apparently required by law. Although gasoline would seem to be an adequate denaturant, perhaps the ethanol must be denatured at the time of manufacture, especially if it is to be transported prior to blending with gasoline. The report states on page 45 that naphtha or another gasoline-like compound may be used. Again, the additions of such compounds increases the complexity of the chemical mixture with unknown effects. Furthermore, the potential for increased public health risk

due to manufacturing and transporting ethanol that could be denatured with a toxic compound does not seem to have been considered.

Response: OEHHA agrees that the type of denaturant that will be used does result in an uncertainty for the exposure assessment. However, as stated in Section 6.6, Uncertainties and Data Gaps, the denaturant is likely to be a gasoline-like material with a similar chemical profile to the hydrocarbon component of the blended fuel. It is therefore unlikely to have a substantial effect on the health impacts of the combined fuel. Its presence as a fraction of a percent in ethanol is unlikely to increase public health risk due to manufacturing and transporting of ethanol.

Comment 9: Finally, the most serious concern is that the data to evaluate the movement of the various gasoline options through the soil and into groundwater are not available. Apparently, the SWRCB has contracted with Lawrence Livermore Laboratories to model a variety of scenarios related to the release of these various gasolines into soil and water.

Response: SWRCB has contracted with Lawrence Livermore Laboratories to more clearly address these water contamination issues. As stated in one of the preceding responses, preliminary screening model results indicate that the cosolvency effect of ethanol is not likely to play a significant role in influencing groundwater transport of benzene or other gasoline components. Also, it should be emphasized that qualitatively, removal of MTBE, which is already a problem with groundwater users, would be an unqualified benefit. Direct effects of ethanol would appear to be minimal even in cases of severe contamination, although the potentially adverse consequences of contamination by the hydrocarbon fraction of the gasoline would remain.

Comment 10: The lack of data in the area of drinking water contamination makes it virtually impossible to review the health risk of ethanol in gasoline. The report acknowledges (page 40) that research has been undertaken to determine if there is a risk of a secondary effect of ethanol, however the report is not specific at this point as to who is doing this research. Is it the same research mentioned above regarding models at Lawrence Livermore Labs? If so, how can they model the effect of a mixture of chemicals when they do not know how those chemicals affect one another? Furthermore, the report appears to suggest that because ethanol is rapidly biodegradable and that it is ingested routinely as a part of the diet that the potential for health effects is low. While this conclusion is likely true, this state will be using millions of gallons of this gasoline each year and because of the potentially severe consequences if adverse effects are not recognized, I feel that ethanol in gasoline should not be approved until the commissioned studies are complete. It seems that MTBE was given approval before studies were performed to determine health risks of the chemical at the level of MTBE that was approved for use. We are now trying to compensate for the results of that decision.

Response: The current OEHHA report presents only a limited evaluation of potential water impacts. Any risk assessment activity is limited by the extent of currently available data, and the conclusions must identify areas of uncertainty as well as areas where

predictions can be made. As stated in an earlier response, these impacts (including determination of any risks of a secondary effect of ethanol) are the subject of research currently being conducted by Lawrence Livermore National Laboratory for the State Water Resources Control Board. OEHHA agrees that these issues are complex and difficult to model. When the results are available, OEHHA will be examining them to determine whether there are any noteworthy public health consequences.

OEHHA's role is to assess the health impact of the alternative fuel formulations, not to make recommendations. Our report, along with the reports of CARB and SWRCB will be presented to the Governor's Environmental Policy Council for consideration. The reviewer's comments regarding the potential use of ethanol in gasoline will be part of the OEHHA report and will also be considered by the Environmental Policy Council.

Comment 11: Overall conclusion: Whenever complex chemical mixtures must be evaluated, there will be problems in data interpretation. However, in this report there are large sections of data that have not been obtained, namely the data on the health effects of soil and groundwater contamination. It is impossible to reasonably assess the potential health risks of ethanol in gasoline if only the atmospheric data is available.

Response: OEHHA thanks Dr. VandeVoort for her comments and agrees that the potential water contamination issues will require further research. As with any risk assessment activity, in order for any evaluation to be undertaken in response to the Governor's Executive Order, it was necessary to do what could be done with the data available. OEHHA feels that both the areas of knowledge and the areas of uncertainty have been fairly presented, thus providing a basis for the Environmental Policy Council's deliberations. As stated above, OEHHA looks forward to obtaining more data, and will provide updated risk assessments as these data are received.

B.2. Public Comments.

The following responses address the comments from the public on the draft Office of Environmental Health Hazard Assessment (OEHHA) document, Volume 5, "Potential Health Risks of Ethanol in Gasoline", which is part of the report to the California Environmental Policy Council titled, "Health and Environmental Assessment of the Use of Ethanol as a Fuel Oxygenate". The following organizations and individuals have submitted comments:

Oxygenated Fuels Association	- comments dated November 30, 1999
Methanex Corporation	- comments dated November 26, 1999
Professor Richard Wilson, Harvard University, on behalf of American Methanol Institute	- comments dated November 30, 1999
Western States Petroleum Association (WSPA)	- comments dated November 30, 1999

The following responses address their comments.

B.2.1. Comments from the Oxygenated Fuels Association, Inc.

Comments on the document “Potential Health Risks of Ethanol in Gasoline” were received from John Kneiss on behalf of the Oxygenated Fuels Association, Inc. (OFA) on November 30, 1999.

Comment 1: In general, OFA believes that the OEHHA assessment of ethanol in gasoline is incomplete because it fails to fully examine the available data on the health effects of ethanol. For example, OEHHA's reliance on secondary reviews of the ethanol database, rather than conducting evaluations of primary scientific literature on ethanol health effects studies, results in understatement of the potential risks associated with increased exposure from expanded use of ethanol in gasoline. As an example, OEHHA has not incorporated into the assessment research showing that exposure to ethanol increases the hematotoxicity of inhaled benzene (Baarson, Snyder, Green, et al. 1982. Toxicol. Appl, Pharmcol. 64(3): 393-404). Such an important potential interaction should be fully considered in the OEHHA assessment, in light of the anticipated increased use of ethanol blending to gasoline in the state.

Response: Due to the short timeframe for this report, OEHHA relied primarily on existing risk assessments for ethanol. OEHHA does not consider that any important interactions have been ignored, taking into account likely concentrations and routes of exposure. However, this is an area of continuing research and OEHHA will continue to be alert for such possible effects.

Comment 2: In several places (first seen on the last line of page 4, and later in Table 1 and Table 7) OEHHA's draft describes the "probability of extra cancer cases occurring in an exposed population..." [emphasis added]. This statement is incorrect. The process used by OEHHA not only estimates the dose-response curves but selects the upper-95% confidence level (95%-UCL) rather than the most likely estimate of risk. The correct interpretation of the 95%-UCL is that it is a limit below which the true risk is likely to be present 95% of the time; and the true risk may be zero. As an estimate, neither the 95%-UCL nor the most-likely-estimate of risk indicate that an increase will occur, only that the chance of a compound-related tumor is increased. OFA recommends changing the language in the report to clarify the conclusions.

Response: OEHHA has been careful to characterize measures such as cancer risk estimates appropriately, following established standard risk assessment methodology. The draft document explains the uncertainties and limitations of these estimates.

Comment 3: The entries under "ethanol" in Table 1 indicate no evidence of carcinogenicity by inhalation. While that statement may be technically accurate, it omits consideration of a substantial body of pertinent information, and runs contrary to some principles of data interpretation. First scientific information indicates that ethanol is known to be absorbed from both the lungs and the gastro-intestinal tract. Furthermore, the organs on which ethanol produces its major toxicity (liver and nervous system) are distal from the portals of entry into the body. Based on the kinetics of ethanol, similar target tissue concentrations are likely to be present for the same doses of ethanol, regardless of route. Thus, toxicity (qualitative and quantitative) observed by ingestion of ethanol should also be similar by inhalation, provided that there is dose equivalency. As noted in the Appendix to the OEHHA draft report (pp 12ff.), human evidence indicates that consumption of large amounts of alcoholic beverages in which ethanol is the major constituent produced cancer in humans - a fact that led URC, and more recently the NTP, to find that alcoholic beverage(s) is a known human carcinogen. Thus, ethanol should be considered a possible human carcinogen by inhalation, and a unit risk should be estimated by inhalation, relying on toxicokinetic information.

Response: Data on the carcinogenicity of ethanol was reviewed in depth under Proposition 65, the State's Safe Drinking Water and Toxics Enforcement Act. Under Proposition 65, the Science Advisory Panel (predecessor of the current Carcinogen Identification Committee) carefully reviewed a large amount of evidence on the carcinogenic effects of ethanol in humans and animals. Their conclusion was that ethanol is a human carcinogen under specific circumstances, namely at high doses and only by the oral route. Therefore, the panel listed "alcoholic beverages, when associated with alcohol abuse" as carcinogenic under Proposition 65. OEHHA followed this assessment in concluding that levels of ethanol predicted to occur in the air or water as a result of its use in gasoline were unlikely to result in a cancer risk to the exposed population.

In comments submitted by Dr. Richard Wilson of Harvard University (letter dated November 30, 1999), Dr. Wilson presents a carcinogenic potency (or unit risk factor) for ethanol that he derived from the rat studies of Holberg and Ekstrom (1995). The potency he presents, 2.0×10^{-4} (mg/kg-day)$^{-1}$, is generally consistent with similar evaluations

conducted for comparative purposes but not used in regulatory assessments. The following conclusions may be drawn from this potency. First, it is one order of magnitude lower than the potency of 1.8×10^{-3} (mg/kg-day)$^{-1}$ calculated by OEHHA for MTBE. The most recent atmospheric concentration estimates provided by CARB indicate that the "best baseline" prediction of population-weighted annual average exposure in the South Coast airshed for 2003 is 8.8 ppb ethanol (in the exposure scenario with ethanol-based fuel containing 3.5% oxygen), and 5.1 ppb ethanol for the continued use of MTBE fuel in 2003. In other words, according to CARB's estimates, the replacement of MTBE by ethanol will result in an increase of 3.7 ppb (6.96 $\mu g/m^3$) in the average exposure to ethanol. Using Dr. Wilson's potency to calculate risk, along with the usual assumptions of 70 kg body weight and 20 m^3 inhaled air per day, a lifetime cancer risk of 4×10^{-7} is derived. This risk estimate is below the 10^{-6} risk level usually regarded as *de minimis*. The total ethanol concentrations in air predicted by CARB, which include some non-fuel related ethanol contributions such as those from stationary sources are also associated with risks less than 10^{-6}. In other words, even if one accepts that ethanol should be regarded as a human carcinogen by the inhalation route, with a linear low-dose response, the risks predicted on this basis from ethanol are negligible. If the *de minimis* criterion is not used to completely discount cancer risks from ethanol, the predicted risk from expected concentrations of MTBE is about fivefold greater than for ethanol. Although MTBE is a weak carcinogen compared to some other fuel-related pollutants such as benzene or butadiene, its predicted contribution to the overall cancer risk is not negligible.

Comment 4: The entries under "MTBE" in Tables 1 and 7 (and also pp 22 and 24, and in the Appendix, pp A-24 ff) indicate that MTBE is treated as a "possible human carcinogen." OFA objects, to this designation, and to the application of the methodology on which OEHHA's position is predicated, since it fails to take full and objective account of the scientific evidence. On numerous other occasions, OFA has provided ample data and justification to support the conclusion that the cancer data are either not applicable to humans based on known modes of action or the result of flawed experimentation or are indeterminate by virtue of study design limitations. Expert groups around the world (including IARC, NTP, Prop 65 CIC have concluded that the evidence is inadequate to characterize MTBE as to its cancer potential for humans. OFA recommends that MTBE be treated not as a carcinogen but should be evaluated for non-carcinogenic chronic toxicity endpoints.

Response: The scientific evidence regarding MTBE toxicity is extensively discussed in OEHHA's Public Health Goal (PHG) risk assessment that was prepared under the California Safe Drinking Water Act, which is referenced in the draft ethanol report. The MTBE risk assessment and the conclusions as to its carcinogenicity went through an open public and scientific peer review process, and have been endorsed by the State's Scientific Review Panel for the purposes of the Toxic Air Contaminant program. The conclusions are also in agreement with the 1998 UC Report (Health and Environmental Assessment of MTBE: Report to the Governor and Legislature of the State of California as Sponsored by SB 521). The Proposition 65 Carcinogen Identification Committee (CIC) was divided on the issue of whether MTBE had been clearly shown to be a

carcinogen. However, the CIC declined to add MTBE to the Proposition 65 list of chemicals known to the state to cause cancer.

Comment 5: OEHHA's draft report (Table 4) provides estimates of air concentration ranges for the compounds selected for this comparison. It is our understanding that the figures for the 1997 baseline scenario (population-weighted annual average) are also modeled despite having empirical data which are more realistic and more reliable than those modeled. We note that, assuming that the correctness of relative concentrations, ethanol increases appreciably in the atmosphere - a situation that was not taken into account in estimating the risks of ethanol in gasoline.

Response: This comment pertains to the work by CARB, which is discussed in detail in their report. However, it is important to note here that the 1997 measured data was used by CARB to calibrate the model for that year.

Comment 6: Table 10 of the draft report fails to include chronic hazard quotients for MTBE for pulmonary irritation. OFA recommends that this be included to complete the comparison. We believe that it will demonstrate that the concentrations of MTBE presently in breathing zone air are unlikely to cause respiratory irritation.

Response: The chronic hazard quotient is based on the most sensitive toxicological endpoints. As described in appendix A of the report, respiratory irritation is known to be associated with acute exposures to MTBE; however, based on the very limited available data on chronic exposures, pulmonary irritation does not appear to be a critical endpoint. The most important constraint on acceptable long-term exposures to MTBE derives from the potential for carcinogenicity.

Comment 7: In Section 6.5 (pp 38), ethanol should be added as a compound of concern. Under the proposed administrative action, ethanol would be present in very large amounts in California, and exposures to ethanol by the general population through air and water over and above that found in food and consumed as alcoholic beverages could be significantly increased.

Response: After careful consideration of the available scientific information, it appears that ethanol is only toxic at very high doses, and under specific circumstances, such as by the oral route. Consideration of the likely fuel-related exposures via contamination of air or drinking water suggest that these would make an insignificant contribution to the general population exposure to ethanol. However, in Table 11 of the report ("Research Needs for More Complete Understanding of the Potential Health Effects of Ethanol in Gasoline"), OEHHA does include ethanol (at low concentrations) in the list of compounds for which basic toxicology information is needed.

Comment 8: The OEHHA draft (pp 39) incorrectly states that health protective goals have been set for ethanol. We are unaware of any such goals being set for ethanol,

despite the presence of "gasohol" over more than two decades of use. At this time, we understand that water utilities have no cost-effective way to monitor the presence of ethanol in ground or surface water.

Response: The report states that there is no regulatory value for ethanol for either air or water (page 42 and appendix A). It is for this reason that OEHHA developed draft health protective concentrations (HPCs) for the purposes of this report. Both measurement and theoretical studies of ethanol in ground and surface water are presently ongoing, and OEHHA is following the results of these studies with interest.

Comment 9: OEHHA incorrectly concludes that the presence of MTBE must be called a "problem." We believe that a balanced view should point out that a very large fraction of MTBE detections are below levels that would present a health risk or that would produce detectable tastes or odors. OFA recommends that OEHHA places the detections of MTBE in groundwater into proper perspective. Examination of California's Department of Health Services monitoring data for drinking water sources (ground water supplies) shows a dramatic decrease in the rate of detections for MTBE, and that only a few isolated instances found levels that exceeded state health protective levels.

Response: It is clear from the Executive Order (D-5-99) that the Governor regards MTBE contamination of the environment as a problem. OEHHA refers the commenter to the California Department of Health Services and the State Water Resources Control Board for data on MTBE monitoring and their evaluation of the impact on water resources.

Comment 10: OEHHA's treatment of the uncertainties in its comparative evaluation was certainly an extensive list. However, it lacked a critical ingredient: namely the impact on the estimates made for each compound selected. Since the uncertainties are likely to vary considerably from one data type (toxicity, exposure) to another among the compounds, the degree of confidence in each conclusion may prove considerable and not be captured by the two point estimates (low and high) given in OEHHA's draft report. OFA recommends that OEHHA estimate the impact of the designated uncertainties in their reported values, and describe the degree of overlap among the values.

Response: For the carcinogens of interest, OEHHA has included a discussion of the degree of confidence in each of the risk estimates based on the uncertainties inherent in the individual potency values. OEHHA agrees that this is important, especially for carcinogens since they drive the overall risk estimates. In addition, further discussion of uncertainties and confidence can be found in the original documentation cited for each of the health assessment values. Very often it is not possible to quantify uncertainty since uncertainty is defined as that which one does not know. Most “uncertainty analyses” in risk assessment actually evaluate variability in measured parameters. The uncertainties noted are due to a lack of data making quantification of uncertainty itself very uncertain.

Comment 11: OEHHA's characterization of ethanol's toxicity (Appendix, ppA.13ff) raises major considerations about its health consequences, and is essential to obtain a fair comparison of risks.

First, OEHHA dues not take into account uniquely susceptible individuals in deriving health protective concentrations, although mention is made that a few such groups exist (other factors such as prescription and over the counter drugs should have been considered yet were not). At a minimum, OEHHA should have included an additional uncertainty factor of 10 to take into account this consideration.

Second, OEHHA makes no mention of infants whose developing nervous systems may be particularly vulnerable to the toxic properties of ethanol. Under the proposed scenario of expanded use of ethanol, these infants might receive doses that pose risks of diminished learning capacity or altered liver function because of added doses of ethanol via the air they breathe and possible ingestion of impacted water resources.

Third, OEHHA makes no mention of a group of individuals whose exposure to ethanol poses a threat to themselves as well themselves, namely recovering alcoholics whose inhalation exposure to ethanol (e.g., during refueling a vehicle) would very likely increase above the background in foods. The exposure levels to ethanol which increase risks to such individuals is uncertain, and OEHHA has not adequately incorporated uncertainty (safety) factors to protect against such risk.

Fourth, OEHHA mentions fetal alcohol syndrome, only to dismiss its significance without data or justification being cited to support this conclusion.

In summary, the draft health protection concentration for ethanol cited in OEHHA's draft report is not substantiated by the scientific evidence and does not represent sound policy of health protection. OFA recommends major revisions to the ethanol discussion and assessment in the Appendix to reflect the full measure of scientific knowledge.

Response: (There appear to be some grammatical peculiarities in the original text of this comment, but OEHHA has endeavored to respond to the intended meaning.)

The draft health protective concentration (HPC) for ethanol includes an uncertainty factor of 10 to account for interindividual variability within the human population, including potentially sensitive human subpopulations (e.g., infants). This standard methodology was also used for MTBE to account for sensitive subpopulations.

Our review of the literature on ethanol uptake shows that very extreme exposures by inhalation are required to achieve absorption of sufficient ethanol to produce a significant impact relative to intake from foods and beverages, or to have any impact on central nervous system function. Such exposures would be extremely irritating and individuals would not stay in the environment long enough to absorb sufficient quantities of ethanol. It is unclear what end-point of concern the comment refers to in relation to recovering alcoholics, although as noted elsewhere such individuals were included among the study populations on which the HPC was based. Similarly, all the evidence concerning fetal alcohol syndrome indicates that this effect results from high maternal exposures such as those relating to the consumption of alcoholic beverages. This issue was discussed by the Proposition 65 Science Advisory Panel’s DART Subcommittee, whose conclusions are

reflected in the exact wording of the listing of “ethanol in alcoholic beverages” as known to the State of California as causing developmental toxicity.

OEHHA notes the commenter’s dissatisfaction with the review of ethanol toxicity. In response to these and other comments received on the possible hazards of ethanol exposure, OEHHA has expanded the review of ethanol toxicity in the report to further explain the basis for the conclusions reached.

B.2.2. Comments from Methanex Corporation

Comments on the document “Public Health Risks of Ethanol in Gasoline” were received from Michael Macdonald, Vice President with Methanex Corporation, in a letter dated November 26, 1999.

Comment 1: Co-solvency and plume length issues detract from improved gasoline containment.

The view of the draft supporting LLNL report, that ethanol can increase gasoline plume lengths, is consistent with the Federal EPA's Blue Ribbon Panel conclusions and with submissions made by Malcolm Pirinie to the UC Davis study public hearings earlier this year. Likewise, the conclusion that ethanol acts as a co-solvent for BTEX in water has also been demonstrated by others (see Journal of Chemical and Engineering Data, Volume 40, No. 1, 1995, pages 315-320, attached).

We believe it is important to note and understand these effects, but we urge you to avoid the trap of making them the issue, when the real issue is gasoline release to the environment. We advocate a strong regulatory and enforcement approach to ensure a reliable, environmentally sustainable fuels infrastructure.

Response 1: Comment noted; State Water Resources Control Board is evaluating co-solvency and plume length.

Comment 2: Don't perpetuate mis-information.

Inclusion of MTBE cancer risk estimates on page 8 of your draft would give any layperson the impression that MTBE is a carcinogen, whereas the approximately 290 scientific papers we have reviewed do not support that assertion.

In appendix A to your draft you referenced just the IARC study, but we suggest that (by itself) the IARC determination that MTBE is "not classifiable" as a carcinogen could also easily be prone to misinterpretation. We request you also include reference to the NTP and Proposition 65 determinations to "not list" MTBE as a carcinogen.

We urge you to fairly represent the body of science available and to not perpetuate the mis-information that has so far clearly characterized the MTBE debate.

Response 2: These issues were extensively discussed in OEHHA's risk assessment of MTBE that was prepared under the California Safe Drinking Water Act (amended Health and Safety Code, Section 116365), which is referenced in the present document. The risk assessment of MTBE and the conclusions as to its carcinogenicity went through an open public and scientific peer review process. It has been endorsed by the State's Scientific Review Panel for the purposes of the Toxic Air Contaminants program. (The conclusions are also in agreement with the UC Report, also referenced in the present Ethanol Report). The Proposition 65 Carcinogen Identification Committee (CIC) was divided on the issue of whether MTBE had been clearly shown to be a carcinogen. However, the CIC declined to add MTBE to the Proposition 65 list of chemicals known to the state to cause cancer.

Comment 3: Aerial benzene may be understated

We have reviewed data from a European oil company showing that ethanol forms azeotropes in gasoline, significantly increasing the total volume and fraction of benzene and olefins in the lower boiling range cuts. Directionally, this would be expected to result in an increase in aerial benzene and olefin emissions. We note on page 31 of your draft report that aerial benzene is a key cancer concern, and separately, that VOC's in general, and olefins in particular, are ozone precursors. Our interpretation of pages 7-8 of CARB's draft supporting report is that aerial benzene concentrations were estimated from actual 1997 field data. As ethanol was not widely used in California at that time, we must assume that the field data did not include any impact from ethanol's azeotropic effects, meaning that ambient levels or emissions of benzene, olefin and total VOC for ethanol-blended gasoline would be understated in CARB's analysis.

Please provide us your understanding of ethanol's effects on aerial benzene, olefin and VOC emissions, and confirm that our understanding of CARB's analysis is correct.

Response 3: Governor Gray Davis's Executive Order D-5-99 requires the California Air Resources Board (CARB) and the State Water Resources Control Board (SWRCB) to conduct an environmental fate and transport analysis of ethanol in air, surface water, and ground water. It requires OEHHA to prepare an analysis of the health risks of ethanol in gasoline, the products of incomplete combustion of ethanol in gasoline, and any resulting secondary transformation products. Since this comment relates directly to CARB's work, we are forwarding your letter to CARB for their consideration. OEHHA is not in a position to speak for CARB. We respectfully defer to them for their expertise in this area.

Comment 4: Co-mingling effect

Ethanol exhibits "non ideal" behavior - one result of this is that a mixture of ethanol - blended gasoline of a given RVP and non-ethanol-blended gasoline of the same RVP will have a higher RVP than the individual gasolines. This is what is known as the "co-mingling" issue with ethanol-blended gasoline, and we could find no reference to it in

CARB's draft supporting report. The obvious expected effect of co-mingling would be further increased VOC emissions.

Please provide us with your understanding of the co-mingling effect and confirm that CARB did not consider it in their analysis.

Response 4: Again, this comment relates directly to CARB's work. We are therefore forwarding your letter to CARB for their consideration. OEHHA is not in a position to speak for CARB. We respectfully defer to them for their expertise in this area.

B.2.3. Comments of Prof. Richard Wilson

Comments on the document "Potential Health Risks of Ethanol in Gasoline" were received from Prof. Richard Wilson (Harvard University), on behalf of the American Methanol Institute on Nov 30th, 1999. The comments address the cancer risk assessment methodology used by OEHHA for ethanol (contrasted to that used for methyl tertiary-butyl ether) and for combustion products such as formaldehyde and butadiene.

Comment 1: In making a comparative risk assessment it is not adequate to take risk assessments for ethanol and MTBE, done at different epochs and by different people. It is necessary to go over the assumptions of the risk assessments and repeat the assessments on a comparable basis. It is here that I find that the OEHHA report is inadequate. In particular, OEHHA uses an old procedure for consideration of the carcinogenicity of ethanol and a more modern and more conservative procedure for estimating the carcinogenicity of MTBE.

In Table 1 page 8 the draft report compares Health Assessment values and Draft Health Protective Concentrations for several chemicals including MTBE and ethanol. In a report sent to OEHHA I commented upon the draft cancer potency assessment for MTBE. I agreed with the Office of Environmental and Health Hazard Analysis (OEHHA) that the potency is not large but came up with a potency (often called a unit risk factor) of $(0.0006\ mg/kg.day)^{-1}$ which is slightly smaller than that selected by OEHHA - the difference being primarily the degree of conservatism. When calculating the unit risk OEHHA assumes a linear dose response relationship at low doses, accepted the somewhat scientifically weak data for inhalation, and ignored (as is usual) the evidence that MTBE reduces the risk of some tumors and may well be a net anticarcinogen. This is what is called a "conservative" approach, which is designed not to understate the risk- I used similar assumptions, but noted that they may not be true.

But the draft report fails to give ethanol an equally pessimistic treatment. First and foremost ethanol is definitely an unequivocally a human carcinogen in the ordinary sense of the word. There is ample evidence that in a significant group of people (cigarette smokers) consumption of ethyl alcohol increases the occurrence of lip cancer. Indeed the synergism between smoking and alcohol is one of the few known examples of a multiplicative synergism that is expected on most multistage cancer models.

Response: The scope and timetable for OEHHA's report on ethanol in gasoline require the use, wherever possible, of existing State risk assessments (which have often taken substantial time to prepare, and have been subject to extensive peer review and

public comment). Failing the availability of State assessments, other authoritative sources such as US EPA regulatory assessments were used when available. The current report relies on assessments of MTBE for the State's Drinking Water and Toxic Air Contaminants (TAC) programs. OEHHA previously responded to Prof. Wilson's comments on the public review draft of the assessment for the TAC program, and was pleased to note that his conclusions were broadly similar to OEHHA's, in spite of minor differences in emphasis and choice of default assumptions. The version of OEHHA's risk assessment of MTBE for the TAC program, which incorporated responses to comments from Dr. Wilson and others, was recently approved by the State's Scientific Review Panel on Toxic Air contaminants. OEHHA's assessment also relies on existing State assessments of ethanol carcinogenicity, in particular the listing as a carcinogen under Proposition 65 of "Alcoholic beverages, when associated with alcohol abuse". This listing reflects agreement with Dr. Wilson's identification of ethanol as a human carcinogen under specified circumstances, and the well-known synergism with smoking. Our reliance on existing risk assessments of ethanol also includes taking note of the listing under Proposition 65 of "Ethyl alcohol in alcoholic beverages" as a developmental toxicant.

Comment 2: Estimates of risk of ingestion of ethanol have been made for at least 30 years. The most important fact about the carcinogenicity of ethanol is that it is unequivocally a human carcinogen - in the simple sense that it has been shown (albeit at a high dose) to cause cancer in people. Ethanol has sometimes been called a co-carcinogen because the evidence that it increased cancers (in humans) was in situations where other chemicals (nicotine) are present. Also the first experiments that showed that alcohol caused an increase in cancer in laboratory animals was an increase in liver cancers (angiosarcoma) when another chemical was present. There is a similar discussion on page A13 of an experiment where N-nitrodiethylamine was present. This led to a model - unverified - that ethanol only causes cancer when these other chemicals present. This model was introduced before the present cancer assessment guidelines and enabled regulators to exclude ethanol from such mandates as Proposition 65. But a careful consideration of possible mechanisms shows that there is just as much reason to accept low dose linearity for ethanol as for most other chemicals.

Response: Ethanol was not "excluded from … (the) mandate (of) … Proposition 65". It was considered by the Science Advisory Panel (predecessor of the current Carcinogen Identification Committee), who carefully reviewed a large amount of evidence as to the carcinogenic and co-carcinogenic effects of ethanol in humans and animals. Their conclusion was that it was inappropriate to recommend a listing implying that ethanol was carcinogenic at low doses or by routes other than oral. The exact wording of the listing (in July 1988) was specified by the Panel, and reflects their assessment of the nature of the hazard. OEHHA followed this assessment in concluding that levels of ethanol predicted to occur in air or water as a result of its use in gasoline were unlikely to result in a cancer risk to the exposed population.

Comment 3: The third line of argument comes from the observation that there is a statistical correlation between carcinogenic potency in rodents and acute toxicity in rodents. Although there exist chemicals for which acute toxicity has been measured and a carcinogenic potency has not been measured or established, there exist no data to

disprove the idea that such chemicals are carcinogenic with a potency given by the approximate correlation which is too weak to be measured. Ethanol is toxic - but weakly so. Indeed the recent tragic history of fraternity parties out of control shows that people have been killed by toxic doses of ethanol. (No one to my knowledge has ever been killed by a toxic dose of MTBE). The weak measured carcinogenicity in male rats is consistent with the Zeise correlation.

Response: OEHHA is familiar with this argument, and has debated the significance of the Zeise correlation in several contexts over the last decade. Various explanations have been proposed for the apparent correlation between carcinogenic potency and quantitative measures of acute toxicity. Some of these relate to proposed mechanisms of carcinogenesis, whereas others point to a purely practical or mathematical reason for the effect. It is not usually accepted as a justification for identifying a particular mechanism (such as increased cell turnover resulting from cytotoxicity) for a carcinogenic effect unless there is additional, independently derived evidence to support such a mechanism. However, in the specific case of ethanol extensive evidence on the nature, occurrence and dose response for hepatotoxicity and other responses after substantial oral doses is available. It may be that this toxicity is an important contributor to the observed carcinogenic and co-carcinogenic effects. Such a mechanistic role for cytotoxicity is usually advanced as a justification for adopting a threshold model for dose-response assessment, rather than the linear approach advocated by Dr. Wilson in his comments. The Science Advisory Panel considered such mechanistic explanations in their conclusions as to the appropriate form of listing for Proposition 65.

Comment 4: … at high doses ethanol given to female rats with no other specific carcinogen present increases the rate of cancers both of the pancreas and pituitary and that in male rats it increases cancer of the liver[4]. An analysis of these data shows that the increase is significant at the level of $P < 0.05$ by the Fisher exact test and by the MSTAGE maximum likelihood program for each of these. Nonetheless ethanol is a very weak carcinogen with a potency of 0.00004, 0.0005 and 0.00003 $(\text{mg/kg body weight})^{-1}$ for each of these outcomes respectively. I take a mean of 0.0002 $(\text{mg/kg body weight})^{-1}$.

Response: OEHHA thanks Dr. Wilson for sharing his analysis, which is generally consistent with similar evaluations conducted for comparative purposes but not used in regulatory risk assessments. The following conclusions may be drawn from Dr. Wilson's calculation. The potency he presents, 2.0×10^{-4} $(\text{mg/kg-day})^{-1}$, is one order of magnitude lower than the potency of 1.8×10^{-3} $(\text{mg/kg-day})^{-1}$ calculated by OEHHA for MTBE. Examination of the CARB tables for levels in the South Coast airshed for 2003 reveals a prediction of 8.8 ppb for the population-weighted annual ethanol exposure in the scenario with ethanol-based fuel containing 3.5% oxygen, as opposed to 5.1 ppb for the continued use of MTBE fuel in 2003. In other words, the replacement of MTBE by ethanol results in an increase of 3.7 ppb (6.96 $\mu g/m^3$) in the average exposure to ethanol. If Dr. Wilson's potency is used, with the usual assumptions of 70 kg body weight and 20 m^3 inhaled air per day, this implies an increased lifetime cancer risk of 4×10^{-7}, below the 10^{-6} level usually regarded as *de minimis.* The total levels of ethanol predicted by ARB are also associated with risks less than 10^{-6}. These total levels include some non-fuel related ethanol contributions such as those from stationary sources. In other words, even if Dr. Wilson's argument is accepted, that ethanol should be regarded as a human carcinogen by

the inhalation route, with a linear low-dose response, the risks predicted on this basis from ethanol are negligible. If the *de minimis* criterion is not used to completely discount cancer risks from ethanol, the predicted risk from expected total air levels of MTBE is about fivefold greater than for ethanol. Although MTBE is a weak carcinogen compared to some other fuel-related pollutants such as benzene or butadiene, its predicted contribution to the overall cancer risk is not negligible.

At the time of preparation of this report, we lack quantitative predictions of possible levels of ethanol in drinking water as a result of fuel contamination of aquifers. However, the qualitative predictions available indicate that any such contamination to a significant degree is very unlikely to occur, due to the rapid biodegradation of ethanol in surface waters and aquifers. Unfortunately MTBE is not subject to such rapid biodegradation, and its potential to contaminate drinking water sources is a matter of record. This therefore leads us to confirm our earlier conclusions that substitution of ethanol for MTBE in fuel would not result in adverse public health consequences, either in regard to the predicted changes in air pollution or based on our current information on the potential for water contamination.

Comment 5: It can be considered a judgement call on whether there is a linear dose response for ethanol and/or MTBE. For MTBE, OEHHA follow the US EPA in claiming to use a linear dose response as a default. It is important to understand one of the main arguments used by the US EPA in 1975 when they assumed default linearity. This was the argument by Crump et al. This is based upon the well known fact that cancers caused by environmental agents are indistinguishable (at present and maybe forever) from cancers that occur naturally. Even though "defense mechanisms" may act to prevent the cancerous effect at low doses, the existence of the naturally occurring cancers (30% of the US population) shows that some natural process has already exceeded the threshold below which the defense mechanism is postulated to occur. Under these circumstances, Taylor's theorem suggests that there should be linearity of response with the environmental dose (which is a dose added above the natural one). Crawford and Wilson[8] showed that this simple argument should apply for other lesions and biological endpoints and is in fact very common.

However OEHHA fails to use the linear dose response default for ethanol, and no good scientific reason is adduced for not using the linear response - only the unsupported statement that it is a "co-carcinogen". Moreover there is no statement of what "co-carcinogen" means or might mean in practice.

Response: OEHHA thanks Dr. Wilson for his restatement of the general principles underlying the use of linear low-dose extrapolation as a default in carcinogen risk assessment. As he observes, these are accepted and used by US EPA and OEHHA, both generally and in the specific case of OEHHA's MTBE risk assessments. However, OEHHA considers that these arguments in favor of the linear default are inapplicable to ethanol, and relies to a substantial degree on the arguments which were considered by the Science Advisory Panel in preparing their recommendation for listing under Proposition 65. Since it was not the purpose of our document on ethanol in gasoline to review or revisit current State risk assessment policy or conclusions, we did not attempt to restate these deliberations. However, it may be of interest to consider Dr. Wilson's potency

calculation as applied to non-fuel sources of ethanol exposure. Ethanol occurs commonly as an ingredient of foods and drinks (other than items usually classified as "alcoholic beverages"), at levels which may be as high as 0.1% (reference). Plausible exposures to ethanol from such sources (which vastly exceed the predictions for atmospheric ethanol pollution) result, using Dr. Wilson's potency, in predictions of substantial cancer incidences of ethanol-related tumors which should be readily observable in the many diet-oriented epidemiology studies of cancer incidence. To the contrary, there are no studies indicating associations between cancer and consumption of fruit juices or other sugar-containing dietary elements, or of the many manufactured foods which contain ethanol as a minor additive or accidental component. Furthermore, the liver and oral cancers to which Dr. Wilson refers as ethanol-related are in fact relatively rare findings in the general population, outside of identified risk groups such as those subject to certain viral infections, or known to ingest enormous quantities of ethanol. If there were a substantial additive contribution (following Crump, Taylor, Wilson and others) to the background cancer incidence from incidental consumption of lower levels of ethanol, one would expect a much more general incidence of ethanol-related cancers, a noticeable clustering of ethanol-related tumors in several easily identifiable dietary classifications, and the appearance of common tumors as well as or instead of rare tumors in the extreme-exposure sub-populations. Since none of these phenomena are observed, it is not unreasonable to characterize Dr. Wilson's prediction as being inconsistent with the available evidence.

Comment 6: The Direct Risk from Either Ethanol or MTBE is Small. (and further explanation)

Response: OEHHA agrees, and states in the document, that the cancer risk from atmospheric MTBE is substantially less than that from certain other pollutants associated with fuel use. It is not clear that this is true in all situations for contamination of water which may be used as a drinking water source, but we lack the quantitative information to evaluate this issue further. OEHHA also calculated and characterized the risk associated with ethanol exposures predicted by the CARB model. Using CARB figures (slightly revised following review) and OEHHA's unit risk for MTBE, the risk from ethanol (using Dr. Wilson's unit risk factor) was found to be approximately one fifth of that predicted from MTBE. Furthermore, the risk predicted was less than the *de minimis* level of 10^{-6}. Finally, OEHHA does not agree with Dr. Wilson's proposal to assume low dose linearity for predicting a cancer risk associated with low inhalation exposures to ethanol. Calculations using his unit risk factor for common dietary exposures to ethanol yield unrealistic predictions. In summary, OEHHA agrees that the direct risk from MTBE as an air pollutant is small, but considers that the direct risk from ethanol as an air pollutant is even lower, and probably negligible.

Comment 7: OEHHA should Discuss the Carcinogenicity of Ethanol. Since the existence or otherwise of a threshold, and the meaning of the work co-carcinogen" is a debatable matter on which reasonable people may differ, the above argument may not be generally accepted. BUT it is sufficiently reasonable that it is grossly improper for OEHHA to issue a document claiming, as it does, to make a comparison between use of MTBE and use of ethanol, without even a discussion of reasonable ranges of opinion.

Response: OEHHA remains very interested in the scientific debates which surround many of these issues, in particular those relating to ethanol, and thanks Dr. Wilson for his contribution to this debate.

Comment 8: The combustion products such as formaldehyde and butadiene. It has long been known that the combustion products from burning of fuels can be much more hazardous than the direct ingestion or inhalation of the fuels themselves. Indeed the purpose of adding MTBE is to reduce some of there combustion products - carbon monoxide and particulates. Moreover the only strong complaint about public health about MTBE is a suggested effect of combustion products. Discussion of combustion products is hard, and inherently uncertain. It is not therefore surprising that this is a weak part of the draft report. But it should be emphasized that the combustion products all of which listed -acetaldehyde, benzene, butadiene, formaldehyde and PAN - are both more toxic and more carcinogenic than either ethanol or MTBE. Although the argument in the earlier pages that the difference in risk from direct exposure to ethanol or MTBE should be insignificantly different from zero, that may not be said of the combustion products for which the risk is 100 times as big (see page 5c of the draft report). The only important differences listed are between the first column and the second and other columns - a calculated difference in risk as shown on page 5c of about 0.00007 (7×10^{-5}) per lifetime. Both the first two columns are for reformulated gasoline with MTBE, but the distinction is an assumed total reduction in emissions between 1997 and 2003. No difference is stated between the risk of combustion products of reformulated gasoline with MTBE than of gasoline with 3.5% ethanol.

The choice between MTBE and ethanol must be based upon other factors. Are the particulates and toxic combustion products reduced more by ethanol than by MTBE? Are there products not considered? It is also necessary when risks are this low to consider the whole life cycle in a Life Cycle Analysis. What is the risk in the chemical plant making MBTE? What is the risk of pesticides in growing the corn to produce the ethanol? Nonetheless the calculated cancer risk from the combustion products is only of the order of 0.0001 (10^{-4}) per lifetime which is the risk level below which most risk assessors would believe the risk is unimportant.

Response: OEHHA agrees with Dr. Wilson that the most important toxic impacts are those of combustion products and atmospheric reaction products derived from fuel use, rather than from effects of either MTBE or ethanol themselves. OEHHA relied on CARB's model to determine what changes would occur if ethanol were substituted for MTBE by 2003. Although there are some changes in the relative contributions of different pollutants, the overall impact of that substitution on public health risk from air pollution is not large. This conclusion is based on those toxic chemicals, particulates, and criteria air pollutants for which we have both model atmospheric data and toxicological information. As noted by Dr. Wilson, and detailed in OEHHA's analysis of uncertainties and research needs, there are still some aspects where we lack sufficient information to reach a conclusion. Some of these (including life cycle analyses) are currently the subject of ongoing research sponsored by various Cal/EPA Boards and Departments. OEHHA notes that the risk level regarded as unimportant for regulatory risk assessment purposes is usually 10^{-6}, not 10^{-4}. On this basis, the risk contribution

from certain fuel-related air pollutants in the South Coast airshed is by no means trivial, and is currently the target of regulatory efforts by CARB to ameliorate these conditions.

B.2.4. Comments from WSPA

Comments on the document "Public Health Risks of Ethanol in Gasoline" were received from Gina Grey of WSPA. Comments are dated November 30, 1999.

Comment 1: The public health impact analysis is incomplete. WSPA believes that OEHHA, by using a standard, default health risk assessment approach focusing on modeled ambient air exposures to ethanol fuel emissions, has neglected to consider potential impacts associated with unexpected circumstances. The analysis needs in depth analysis and evaluation to look beyond the easily quantified, expected exposures. Several examples of potential, unevaluated problem areas are provided in our comments, but, obviously, others exist and should be considered.

Response: Lifecycle analysis and consequences of accidental releases of various types are the subject of research by Lawrence Livermore National Laboratory for the State Water Resources Control Board (SWRCB). At the time of preparation of this report, these analyses were incomplete; however, when the results are available OEHHA will be examining them to determine whether there are any noteworthy public health consequences.

Comment 2: OEHHA's analysis fails to uniformly apply current public health policies. OEHHA has defined MTBE as a human carcinogen, while ignoring the known potential for ethanol to cause cancer in humans. WSPA believes that neither of these chemicals should be considered to cause cancer in humans at low environmental levels. Nevertheless, OEHHA should not rely on a major shift in California's cancer policy paradigm when evaluating ethanol and should evaluate both chemicals, ethanol and MTBE, using the same criteria. Applying a less rigorous carcinogenicity analysis to ethanol results in an apple and orange comparison that skews the overall risk assessment results.

Response: In preparing this report OEHHA used, wherever possible, existing risk assessments for specific chemicals that have been developed under other California regulatory programs. These assessments have been subject to extensive peer review and public comment.

In the case of MTBE, OEHHA relied on risk assessments that were developed under California's Safe Drinking Water Act (amended California Health and Safety Code, Section 116365) and the Toxic Air Contaminant Program (California Health and Safety Code 39660 et seq.). These risk assessments conclude that MTBE is a potential human carcinogen.

OEHHA has not ignored the known potential for ethanol to cause cancer in humans. This issue is discussed at greater length in the response to comments by Dr. Richard Wilson of Harvard University. OEHHA relied on the existing State assessments of ethanol carcinogenicity, in particular the listing as a carcinogen under Proposition 65, the

State's Safe Drinking Water and Toxics Enforcement Act. Ethanol was considered by the Science Advisory Panel (predecessor of the current Carcinogen Identification Committee), who carefully reviewed a large amount of evidence as to the carcinogenic effects of ethanol in humans and animals. Their conclusion was that ethanol is a human carcinogen under specified circumstances, namely at high doses and only by the oral route. Therefore, the panel listed "alcoholic beverages, when associated with alcohol abuse" as carcinogenic under Proposition 65. OEHHA followed this assessment in concluding that levels of ethanol predicted to occur in the air or water as a result of its use in gasoline were unlikely to result in a cancer risk to the exposed population.

In comments submitted by Dr. Richard Wilson of Harvard University (letter dated November 30, 1999), Dr. Wilson presents a carcinogenic potency (or unit risk factor) for ethanol that he derived from the rat studies of Holberg and Ekstrom (1995). The potency he presents, 2.0×10^{-4} (mg/kg-day)$^{-1}$, is generally consistent with similar evaluations conducted for comparative purposes but not used in regulatory assessments. The following conclusions may be drawn from this potency. First, it is one order of magnitude lower than the potency of 1.8×10^{-3} (mg/kg-day)$^{-1}$ calculated by OEHHA for MTBE. The most recent atmospheric concentration estimates provided by CARB indicate that the "best baseline" prediction of population-weighted annual average exposure in the South Coast airshed for 2003 is 8.8 ppb ethanol (in the exposure scenario with ethanol-based fuel containing 3.5% oxygen), and 5.1 ppb ethanol for the continued use of MTBE fuel in 2003. In other words, according to CARB's estimates, the replacement of MTBE by ethanol will result in an increase of 3.7 ppb (6.96 $\mu g/m^3$) in the average exposure to ethanol. Using Dr. Wilson's potency to calculate risk, along with the usual assumptions of 70 kg body weight and 20 m^3 inhaled air per day, a lifetime cancer risk of 4×10^{-7} is derived. This risk estimate is below the 10^{-6} risk level usually regarded as *de minimis*. The total ethanol concentrations in air predicted by CARB, which include some non-fuel related ethanol contributions such as those from stationary sources are also associated with risks less than 10^{-6}. In other words, even if one accepts that ethanol should be regarded as a human carcinogen by the inhalation route, with a linear low-dose response, the risks predicted on this basis from ethanol are negligible. If the *de minimis* criterion is not used to completely discount cancer risks from ethanol, the predicted risk from expected concentrations of MTBE is about fivefold greater than for ethanol. Although MTBE is a weak carcinogen compared to some other fuel-related pollutants such as benzene or butadiene, its predicted contribution to the overall cancer risk is not negligible.

Comment 3: OEHHA's analysis fails to quantify potential water impacts. The introduction of large amounts of ethanol into California's gasoline supply could have a number of direct and indirect impacts on water quality. OEHHA has not completed the analysis and a large number of questions must be answered. Several of the missing portions of the analysis have been highlighted by OEHHA as areas requiring additional data or study. WSPA concurs, but believes that the data should be collected and evaluated before a risk assessment is generated.

Response: The present analysis is based on available information, and therefore can only provide qualitative evaluation of potential water impacts. These impacts are the subject of research currently being conducted by Lawrence Livermore National Laboratory for the State Water Resources Control Board (SWRCB). At the time of preparation of this report these analyses were incomplete, but when the results are available OEHHA will be examining them to determine whether there are any noteworthy public health consequences.

Comment 4: OEHHA's analysis does not quantify uncertainty. The input data and assumptions used in OEHHAs analysis have a high uncertainty associated with them. Everything from estimates of concentrations of chemicals in the environment, to the toxicological endpoints used to characterize potential public health risks, has varying degrees of uncertainty. While some inputs may have low uncertainty, others are likely to have very high levels. The level of uncertainty could very well be a more important metric for evaluating the potential impacts of ethanol in gasoline than the absolute values themselves and OEHHA needs to provide some quantification of these uncertainties.

Response: The uncertainty in exposure estimates is discussed in greater detail in the accompanying report by CARB, and OEHHA cites the plausible range of values from their predicitions, and quotes their descriptive notes where appropriate. Source documents for toxicological standards from California or U.S. EPA describe uncertainty and variability issues in detail. OEHHA has been careful to characterize measures such as cancer estimates appropriately, following established practice in deriving 95% upper confidence limits. Where health protective levels were derived for this document, the size and nature of uncertainty factors used are described. As more information becomes available and measured emissions data are obtained, OEHHA will be continuing to review these and may reach additional conclusions as a result.

Comment 5: Resolution of research needs and outstanding issues. As part of its analysis, OEHHA has identified a number of data needs and issues requiring resolution. WSPA believes that many of these data needs or issues are of sufficient import that the analysis of the potential public health and environmental impacts of ethanol in gasoline can not be completed until this information is available.

Response: The present assessment is not intended to be a final assessment, but rather the best analysis possible with currently available data. As further information becomes available, OEHHA will be continuing to examine the health impacts of fuel-related toxics in air and water. Any additional information on the toxic effects or environmental occurrence of fuel-related pollutants which the commenter (or others) currently possess, or obtain in the future, will be welcomed as a contribution to this ongoing review.

Comment 6: In extensive written comments, WSPA requested the development of key information that has still not received the appropriate attention. For example, WSPA requested a clear description of the risk management process that will be used by the

agencies and the EPC for the evaluation of ethanol as a replacement for MTBE. This information has still not been developed to the detriment of the analyses conducted by the individual agencies. There does not seem to be a clear picture of how the information developed will be utilized. Worse, the tone of the most recent workshop suggested that the completed analyses were a proforma exercise.

Response: The OEHHA report was produced at the direction of Cal/EPA responding to the Governor's executive order. The report was produced using an independent and objective approach with no preconceptions or direction as to its conclusions. In regards to the request for a description of the risk management process that will be used by Cal/EPA and the EPC, that is beyond the scope of the present health effects assessment.

Comment 7: A complete conceptual life-cycle model of the manufacture, distribution and use of ethanol in the blending of fuels and the storage, distribution and use of those blended fuels. The OEHHA analysis presents a regulatory-style analysis of public health impacts that is limited to exposures of evaporative and tailpipe emissions in ambient air. Although the agency's workplan suggested it would also evaluate compounds present in drinking water, the draft document approaches drinking water in a limited, qualitative manner only. There is no analysis of any number of potential other sources of exposure that could change depending upon the specific use of an oxygenate. These include, for example, manufacturing facility emissions, blending emissions, and storage facility emissions. Without this type of analysis it will not be possible to form any supportable conclusions concerning potential public health impacts.

Response: According to CARB's accompanying chapter regarding the exposure scenarios and data, the comment's assertion that only tailpipe and evaporative emissions were considered is inaccurate. Fugitive emissions from fueling activities are included in the CARB analysis.

A full life-cycle analysis could not be done by the deadline. However, the report by the SWRCB evaluates a number of scenarios representing storage and distribution. OEHHA will be evaluating this type of information in the future.

Comment 8: The sources and degree of uncertainty as well as recommendations for resolving uncertainty need to be provided. The OEHHA analysis presents estimates of risk without quantification of potential uncertainty. The document explains that this is acceptable because the estimates of risk are relative and it is the relative difference between the fuels that is important. This is unacceptable from a risk management perspective. Not only is it likely that the uncertainty in the exposure estimates is high (and also the relative uncertainty between various fuel types), but also that the uncertainty in estimates of potential risk due to uncertainty in the health criteria is extremely high. The latter is, of course, purposefully biased in the risk assessment process in a health conservative manner so that the actual value may be substantially less, but not higher. Without an analysis of uncertainty there is no indication by which the validity of the results for comparison between scenarios can be ascertained.

Response: As noted above, the uncertainty in exposure estimates is discussed in greater detail in the accompanying report by CARB, and OEHHA cites the plausible range of values from their predicitions, and quotes their descriptive notes where appropriate. Source documents for toxicological standards from California or U.S. EPA describe uncertainty and variability issues in detail. OEHHA has been careful to characterize measures such as cancer estimates appropriately, following established practice in deriving 95% upper confidence limits. Where health protective levels were derived for this document, the size and nature of uncertainty factors used are described. As more information becomes available and measured emissions data are obtained, OEHHA will be continuing to review these and may reach additional conclusions as a result.

In addition, it is important to note that not all sources of uncertainty result in risk estimates higher than the actual risk. As noted in OEHHA's report, many of the acknowledged uncertainties affect risk estimates to the same extent for the different fuel scenarios. It is for this reason that our confidence in relative predictions is greater than our confidence in the absolute predictions.

Comment 9: OEHHA should evaluate taste and odor effects on groundwater. OEHHA did not analyze potential taste and odor effects on groundwater due to the presence of ethanol breakdown products or the potential for ethanol to alter the effect of gasoline components on the taste and odor of water. This in turn is directly tied to water based criteria that could lead to unacceptable water quality. This information is critical for any risk management decision. The simple question of "'How much ethanol (or breakdown products) in drinking water would be considered unacceptable?" must be answered in order to evaluate the significance of environmental contamination.

Response: At present, OEHHA has received no indication from the SWRCB that contamination of drinking water by ethanol at any level detectable by chemical analysis, let alone taste and odor, is likely. However, if and when more detailed information is available on this point OEHHA will determine whether any further evaluation of toxicological or sensory (organoleptic) properties is needed.

Comment 10: The public health impact analysis is incomplete. OEHHA's analysis applies standard health risk assessment policy/methods to modeled ambient air concentrations of a select list of chemicals of concern. Yet, simple inspection of the modeled concentrations without the health risk assessment provides the same conclusions: there are no differences between the fuel types. This type of approach does not do justice to the potential ramifications, if an unforeseen problem develops.

The OEHHA analysis appears to assume that the key (if not sole) impacts from ethanol-based oxygenated fuels will occur in ambient air from normal use. Other potential problem areas do not appear to have been explored and are not quantified?

A complete analysis is needed. For example, could hot soak emissions plus tailpipe emissions at low speed from ethanol-based fuels lead to higher concentrations of irritants

(or carbon monoxide) inside parking structures? Or, will the consumer refueling with ethanol-based fuel notice a different smell or a minor nasal irritation that would lead to perceptions of health concerns similar to what happened with MTBE in several states? It is common knowledge that there is the potential for toxic interactions with very low levels of ethanol for individuals taking the prescription drug disulfiram (Antabuse). Could these individuals be a sensitive population for ethanol exposure and, if they are, what restriction on levels of ethanol in drinking water would be required to provide adequate health protection? Numerous questions such as these should have been posed and answered in a quantitative manner within the assessment. The basis for eliminating a potential problem from consideration should be clearly stated. Without this type of analysis, the potential for a currently unrecognized significant public health problem (or perceived problem) is high.

Response: CARB has examined different scenarios with various vehicle types and use patterns, and is continuing to research these issues as part of their long-standing programs for study and regulation of mobile and stationary sources of air pollutants. OEHHA will be continuing to work with CARB to examine possible public health consequences of any such situations.

The ethanol irritation data examined in developing a draft health protective concentration (HPC) for the purposes of this report specifically included a group of subjects receiving disulfiram treatment for alcoholism. OEHHA risk assessment policy includes application of an uncertainty factor (default value of 10) for inter-individual variation in the human population, which is designed to allow for the possibility of sensitive sub-populations among those exposed to general environmental contaminants. Low levels of ethanol are common in many natural and manufactured food products without causing apparent problems to the general population, and these may involve considerably higher exposures to ethanol than are anticipated as a result of its incorporation in fuel.

Comment 11: OEHHA's analysis fails to uniformly apply current public health policies. Over the last twenty years, California EPA and its predecessor agencies have firmly established a carcinogen assessment policy. This policy has dictated in a highly inflexible manner that chemicals with data suggestive of a potential cancer risk be evaluated as if they do, in fact, represent a cancer risk. In quantitative analyses (i.e., health risk assessments), no allowance is made for the weight of evidence and there is no established mechanism for incorporating alternatives to the default linear extrapolation and use of the statistical upper-bound of cancer potency estimates. Exceptions, if any, to this are rare. This policy dictates that there is no dose (exposure) other than zero that is without risk.

The evaluation of MTBE exposures in the OEHHA analysis aggressively follows this policy; California leads the world in ascribing human carcinogenic risk to MTBE exposures. For example, the International Agency for Research in Cancer (IARC) recently described the carcinogenic potential for MTBE as "inadequate evidence in humans", "limited evidence" in experimental animals" and "not classifiable as to its carcinogenicity to humans" (IARC, September 30, 1999). Nevertheless, OEHHA,

consistent with the California policy (although at odds with the failure to list under Proposition 65), evaluates MTBE at low levels in ambient air as if it is a human carcinogen.

Although we strongly believe that the available data does not support the regulatory conclusion that exposures to environmental levels of MTBE represents a cancer risk, the decision to so treat MTBE is consistent with the state's ultra-conservative approach. However, and although we agree with OEHHA's assessment of the lack of cancer risk associated with low environmental exposures to ethanol, its failure to incorporate the potential carcinogenicity of ethanol into the analysis by development of a cancer potency slope using the consistently applied methodology is an entirely inappropriate regulatory paradigm shift. Ethanol is a known human carcinogen; IARC identifies ethanol as a known human carcinogen and ethanol (in alcohol beverages) is listed under California's Proposition 65. Under these circumstances, OEHHA should either apply the same rigorous and ultra-conservative cancer risk assessment methodology it uses to evaluate MTBE, or provide a solid scientific rationale for not doing so. OEHHA's apparent reliance on the fact that ethanol is commonly found in the environment, that regulatory bodies do not seem to be concerned over low ethanol exposures and that the carcinogenic effects are seen only at high exposure levels consistent with the induction of other toxicity is not sufficient. Consider the recent development and application of a cancer potency slope for exposure to crystalline silica by OEHHA for a Safe Use Determination under Proposition 65. Crystalline silica is another agent that is ubiquitous in the environment and appears to only cause cancer at high exposure levels associated with silicosis. OEHHA has previously even noted that the carcinogenic effect of crystalline silica appears to operate under a threshold mechanism. Nevertheless, OEHHA applied the standard multi-stage extrapolation to generate a cancer potency slope for the Safe Use Determination. Why has it not done so in the case of ethanol?

Response: As stated in the response to comment 2, it was necessary for OEHHA to rely on existing risk assessments for specific chemicals that have been developed under other California regulatory programs. OEHHA has not ignored the known potential for ethanol to cause cancer in humans. OEHHA relied on existing State assessments of ethanol carcinogenicity, in particular the listing as a carcinogen under Proposition 65, the State’s Safe Drinking Water and Toxics Enforcement Act. Ethanol was considered by the Science Advisory Panel (predecessor of the current Carcinogen Identification Committee), who carefully reviewed a large amount of evidence as to the carcinogenic effects of ethanol in humans and animals. Their conclusion was that ethanol is a human carcinogen under specific circumstances, namely at high doses and only by the oral route. Therefore, the panel listed “alcoholic beverages, when associated with alcohol abuse” as carcinogenic under Proposition 65. OEHHA followed this assessment in concluding that levels of ethanol predicted to occur in the air or water as a result of its use in gasoline were unlikely to result in a cancer risk to the exposed population.

Comment 12: OEHHA's analysis fails to quantify potential water impacts. OEHHA's justification for not analyzing water impacts is meretricious in that it presumes that because the Regional Boards will eliminate the use of groundwater impacted by

chemicals, then there are no chronic exposures and no potential impacts. The same would, of course, be true of MTBE.

OEHHA further discounts groundwater impacts from ethanol because it degrades. However, as indicated in Volume 4, Chapter 3 of the report entitled "The Effect of Ethanol on BTEX Biodegradation and Natural Attenuation", ethanol degrades to volatile fatty acids (e.g., acetic acid). These acids would likely have secondary effects, e.g., changes in taste and odor. Even under OEHHA's presumption that water districts would close wells to eliminate exposures, there is still the larger issue of "What levels of ethanol and/or degradation products will require well closure?" Without health and/or organoleptic criteria by which modeled concentrations can be evaluated, it will not be possible to determine potential impacts to groundwater. To assert that there will be none, absent an evaluation, is not supportable.

Nor does OEHHA consider mutual solvency and how it might impact groundwater. For example, the presence of ethanol would increase solubility of chlorinated solvents already present in soil and groundwater. The presence of ethanol also appears to alter biodegradation dynamics for BTEX by decreasing degradation (See Volume 4, Chapter 2 - A Critical Review: The Effect of Ethanol in Gasoline on the Fate and Transport of BTEX in the Subsurface). This in turn could impact the influence of other chemicals, as well as petroleum hydrocarbons, at currently impacted sites (i.e., increase plume size). It should be noted that the absence of this type of evaluation in the report is an example of what is lacking, as discussed in the first comment.

Response: As noted above (see response to comment 3), our report presents only a preliminary, qualitative evaluation of potential water impacts. The potential water impact issues raised here by the commenter are the subject of research currently being conducted by Lawrence Livermore National Laboratory for the State Water Resources Control Board (SWRCB). At the time of preparation of this report these analyses were incomplete, but when the results are available OEHHA will be examining them to determine whether there are any public health consequences.

Comment 13: OEHHA's analysis does not quantify uncertainty. While OEHHA discusses sources of uncertainty (e.g., extrapolation from animal data to humans), the analysis does not attempt to quantify uncertainty. Yet, it is critical for the risk manager to understand both the sources of uncertainty as well as the potential magnitude and direction of that uncertainty. By relying upon standard, default health risk assessment techniques, OEHHA has excluded valuable risk management information. For example, OEHHA uses the statistical upper-bound in describing the potential carcinogenicity of chemical emissions (except for ethanol). This is standard policy. Missing, however, is information on the most likely estimate of cancer risk both from a statistical standpoint as well as a "weight of evidence" perspective. While OEHHA does mention that actual risks could be substantially lower, they provide no basis for evaluating, for example, whether equivalent theoretical risks due to exposure to benzene and butadiene represent an equivalent potential for actual risks. Other uncertainties arise from the emission estimates, the estimates of ambient air concentrations, the worst-case exposure scenarios rather than likely exposure scenarios, and the exclusion of variations in exposures

through OEHHA's use of standardized population-weighted exposures. The need to include quantification of uncertainty in the analysis is also important because of the relative nature of the analysis performed by OEHHA. Currently, the health risk assessment shows no difference between the various fuel scenarios. However, if one scenario has greater uncertainty than other scenarios, then that may be the information most critical to the risk management decision.

For some time, health risk assessment methodology has been utilizing stochastic techniques for quantifying risk in which the uncertainty or variability of assumptions are explicitly incorporated into the analysis. These techniques work equally well for toxicity endpoints as well as exposure assumptions, and California EPA has expended extensive effort to develop models utilizing stochastic techniques and has promoted their use. OEHHA should use these existing techniques to quantify uncertainties and incorporate considerably more information into the analysis.

Response: As noted in a previous response, additional details on cancer risk assessments are available in the existing chemical-specific risk assessment documents to which OEHHA referred in developing the assessment for ethanol in fuel. CARB's accompanying report deals with selection of scenarios (which in the case of the cancer predictions are estimated annual averages, not worst-case scenarios), and model uncertainties in the prediction of exposures. OEHHA's cancer risk assessment policy includes consideration of uncertainties, and the use of a weight of evidence approach. The properties of various statistical measures available for expressing cancer risk estimates (including the unsuitability of the "maximum likelihood estimate" due to its statistical instability in the standard linearized multistage model) have also been the subject of very extensive discussion in the scientific literature. These considerations are incorporated in U.S. EPA and California risk assessment guidelines. OEHHA refers the commenter to these sources for clarification.

OEHHA is in the process of developing guidance for utilizing stochastic techniques in exposure assessment, and may consider using this methodology more extensively in future assessments of fuel-related health risks. However, the stochastic techniques for quantifying exposure are not, as implied by the comment, readily applicable to "toxicity endpoints". The stochastic analysis requires extensive data on specific data on specific parameters in a model, and as developed by Cal/EPA, only defines variablity. The uncertainties in "toxicity endpoints" and health criteria are far less amenable to a credible stochastic assessment.

Comment 14: Resolution of research needs and outstanding issues. OEHHA identified a number of data needs, which have been separated into areas of research and issues. Many of these components have previously been identified by WSPA. While WSPA does not believe all of the identified areas are of equal merit or even useful for differentiating between potential public health impacts of fuels (e.g., toxicology of alkylates), several are critical. For example, OEHHA identified:

- Development of health assessment values for ethanol,
- Identification of breakdown products in water,
- Impacts of transportation accidents,

- Impacts of watercraft,
- Information on localized "hot spots", and
- Life-cycle analysis to determine overall exposure from production, use and disposal of motor fuels.

WSPA concurs that these are key unknowns. However, we want to emphasize the agency should provide recommendations such as: what data/studies are needed, how long they would likely take, and what expertise is needed to accomplish their acquisition. Until the information is available to either answer these key questions or incorporate the results into the analysis, any conclusion regarding the potential public health impacts of ethanol in gasoline relative to the other potential fuel scenarios will not be accurate or complete.

Response: OEHHA believes its analysis is accurate, based on the currently available data. As more data become available, the assessment of public health impacts of fuel components will be extended to reflect any new findings and conclusions. OEHHA would be pleased to discuss the need for additional studies and their possible scope with any interested parties. However, such discussions are outside the scope and timescale determined by the Governor's Executive Order for this document.