Comments of Sharon H. Kneiss on behalf of the American Chemistry Council.

Comment 1:
As a preliminary matter, the Panel notes that this draft document for ethylbenzene is intended to supplement an existing OEHHA evaluation of potency factors for substances listed under the Toxic Air Contaminant Identification and Control Act (TAC Act), and that OEHHA intends to submit the draft document for review by the Scientific Review Panel established pursuant to that statute. The TAC Act declares that,

“The identification and regulation of toxic air contaminants should utilize the best available scientific evidence gathered from the public, private industry, the scientific community, and federal, state, and local agencies.”

In conducting health effects evaluations under the TAC Act, OEHHA is required to "consider all available scientific data, including, but not limited to, relevant data provided by ... international and federal health agencies, private industry, academic researchers, and public health and environmental organizations," and OEHHA is specifically directed to "assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors." Because the current version of the OEHHA Document does not consider a number of highly relevant pieces of scientific information that establish the likely MOA for the carcinogenic effects of ethylbenzene in laboratory animals, and that demonstrate that OEHHA has selected the wrong methodology for determining a unit risk factor for ethylbenzene, OEHHA must withdraw the draft document, fully evaluate the missing information, and revise the draft document to reflect that evaluation before submitting it for review by the Scientific Review Panel.

Response:
OEHHA disagrees with the assertions of inadequate consideration of scientific data in this comment. OEHHA has reviewed the original studies cited by the commenter or referenced in the attachments. Some specific additions to the document are being made in response to subsequent comments from this and other sources. The principal change is to follow the suggestion made by this commenter to use the PBPK model for the Fischer 344 rat published by Dennison et al. (2003), rather than the previously used model for the Sprague-Dawley rat.

Comment 2:
All of the important scientific information that is missing from the OEHHA Document is either discussed in, or was prepared or collected for, the submission by the [ACC] Panel to a Peer Consultation organized by the non-profit organization Toxicology Excellence for Risk Assessment (TERA) as part of the U.S. Environmental Protection Agency (EPA) Voluntary Children's Chemical Evaluation Program (VCCEP). This Peer Consultation was convened by TERA on February 22-23, 2007, in Erlanger, Kentucky. The submission by the Panel to this VCCEP Peer Consultation includes an extensive, comprehensive, and authoritative discussion of the same subject matter that is addressed in the OEHHA Document. Although the Panel's submission was available for public review, and the deliberations of the Peer Consultation were both open to the public and available on a simultaneous web cast, it does not appear that OEHHA considered this extensive source of pertinent scientific information when it prepared the
OEHHA Document on ethylbenzene.

Response:
OEHHA is well aware of the discussions which are presented in the report of the VCCEP Peer Consultation, and of the original published literature cited in that report. The fundamental area of disagreement between the VCCEP panel and OEHHA concerns the evaluation of likely modes of action for ethylbenzene carcinogenicity, and risk assessment decisions based on that analysis, as further discussed below (comment 3). OEHHA has not referenced this data review directly in the draft document since the emphasis of OEHHA risk assessments is on primary data sources. Only reviews and evaluations by bodies with clearly established authority, such as IARC, or program materials for U.S. EPA which have been reviewed by their Science Advisory Board, are cited or quoted directly. The VCCEP Peer consultation does not have this level of review and authority.

Comment 3:
The attached report prepared by the Sapphire Group includes detailed technical comments on the OEHHA Document, focusing on two key areas: cancer mode-of-action and the physiologically-based pharmacokinetic model for ethylbenzene proposed by OEHHA. In the Sapphire Group report, the cancer mode of action is discussed for each tumor type using the ILSI RSIIIPCS framework, as suggested by the VCCEP Peer Consultation Group. The Sapphire Group scientists who prepared the attached document were responsible for the corresponding sections of the Panel's VCCEP submission, and thus are most familiar with the issues involved. The key mode of action arguments set forth in this report are summarized below.

The most critical deficiencies in the OEHHA Document involve the failure of OEHHA to do an adequate analysis of the MOA for cancer induction by ethylbenzene. Although the OEHHA Document cites the framework developed by EPA for evaluating evidence on potential MOAs, OEHHA has not properly utilized and applied the ILSI RSIIIPCS framework and "modified Hill criteria" adopted by EPA in that framework. These criteria require that each potential MOA for cancer induction be evaluated for strength of association, consistency of association, specificity of association, dose-response concordance, temporal relationship, and coherence and plausibility.

The Panel has extensively evaluated each MOA using the ILSI RSIIIPCS framework and Hill criteria, including the hypothesis of direct genotoxicity, in its VCCEP submission and also in the attached report. This evaluation indicates that the hypothesis of direct genotoxicity does not satisfy the modified Hill criteria, and that selection of a linear dose-response model is inappropriate for all of the animal tumor types induced by ethylbenzene. This evaluation also demonstrates that chronic progressive nephropathy (CPN) is the most reasonable MOA for the rat kidney tumors, that the rationale of OEHHA for rejecting this MOA is not supportable, and that these tumors are of questionable relevance to humans. This evaluation specifies potential MOAs for the mouse lung tumors and for the mouse liver tumors which OEHHA has not considered, and which satisfy all of the modified Hill criteria. This evaluation also concludes that the mouse lung tumors are those with the greatest potential relevance to humans, and that the risk to humans based on these tumors should be assessed by using a margin of exposure to derive a reference concentration (RfC) for ethylbenzene.
The OEHHA Document correctly characterizes a number of genotoxicity studies for ethylbenzene. The only one of these genotoxicity studies that was not negative was a mouse lymphoma cell test in which ethylbenzene was reported to induce mutations at a dose which was the highest non-lethal dose tested and also caused pronounced cytotoxicity. The OEHHA Document cites this older study, but does not consider a recent repeat of the mouse lymphoma test with ethylbenzene, which was negative. This new study reinforces the conclusion that ethylbenzene is not genotoxic, and that it is inappropriate for OEHHA to use a model in deriving a cancer unit risk factor for ethylbenzene that implicitly assumes direct genotoxicity. A recent review article also concludes that ethylbenzene is not genotoxic, and the VCCEP Peer Consultation participants did not disagree with this conclusion. OEHHA states that it is appropriate to use an assumption of low-dose linearity because "the metabolism data clearly show the formation of epoxides and related oxidative metabolites, which could potentially be involved in a genotoxic mechanism..." This conclusion by OEHHA is flawed because it is contrary to the overwhelming weight of the scientific evidence, which demonstrates that ethylbenzene is not genotoxic.

The Panel recognizes that OEHHA will use a linear dose-response model to derive a cancer potency value "based on either the demonstration of a mode of action (MOA) supporting a low dose linear dose-response or insufficient evidence supporting an alternative nonlinear low dose response leading to a NOAEL or margin of exposure for the observed tumor response." From the OEHHA Document, it is clear that OEHHA did not consider the evidence supporting a nonlinear MOA for the tumors induced by ethylbenzene in the animal models to be sufficient. The Panel believes that OEHHA has inappropriately rejected CPN as the MOA for the rat kidney tumors. The Panel notes that OEHHA has not yet considered either of the MOAs proposed by the Panel for the mouse lung and the mouse liver tumors. As the attached report demonstrates, these proposed MOAs satisfy all of the modified Hill criteria, and should therefore be recognized.

With respect to the proposed MOA of CPN for the rat liver tumors, the OEHHA Document rejects this MOA, which was first proposed in a 2002 paper that observed that ethylbenzene induces renal tumors in conjunction with increased incidence and severity of CPN. The decision by OEHHA to reject this MOA is based primarily on observations in a retrospective evaluation of National Toxicology Program (NTP) chronic studies that is not specific to ethylbenzene. In contrast, another recent review not considered by OEHHA specifically supports the CPN hypothesis for ethylbenzene. The Panel has demonstrated that this MOA satisfies all of the modified Hill criteria. Although a final report has not yet been issued for the VCCEP Peer Consultation, it is important to note that none of the participants in that Consultation expressed any disagreement with the Panel's conclusions that tumor production in rat kidneys is attributable to CPN and that available evidence indicates that this effect in rats is not relevant to humans. OEHHA should not base its assessment on this tumor type.

The Panel has also proposed a MOA for induction of mouse liver tumors and a MOA for induction of mouse lung tumors by ethylbenzene, which were not considered in the OEHHA Document. For mouse liver tumors, the proposed MOA is hepatic enzyme induction resulting in increased cell proliferation. This MOA satisfies all of the modified Hill criteria, and appears not to be relevant to humans. None of the participants in the VCCEP Peer Consultation expressed any disagreement with this proposed MOA or with the Panel conclusion that available evidence
indicates it is not relevant to humans.

For mouse lung tumors, the Panel has proposed a MOA of cytotoxicity of ethylbenzene metabolites at high doses, resulting in regenerative cell proliferation. This proposed MOA satisfies all of the modified Hill criteria, and is the most likely mechanism of those proposed to be relevant to humans. The Peer Consultation participants did not disagree with using the mouse lung tumors for cancer risk assessment. The Panel agrees with OEHHA that the high background incidence of testicular tumors in rats makes the increased incidence of this tumor type at the highest dose for ethylbenzene inappropriate for use in human risk assessment. The Panel believes that OEHHA should use the mouse lung tumor as the basis to derive its unit risk factor for humans. Since ethylbenzene is not genotoxic, OEHHA should calculate an RfC using a margin of exposure rather than utilizing a linear dose-response model.

In its document, OEHHA presents unit risk values for ethylbenzene for each animal tumor type induced by ethylbenzene using both linearized multi-stage and benchmark dose methods. It should not be surprising that both of these methods yield similar results, because both methods incorporate linear extrapolation. This analytic approach is misleading for ethylbenzene because the range of estimates provided by OEHHA does not reflect the single factor that would have the greatest effect on the unit risk figure, which is the choice of a linear or nonlinear model. The VCCEP Peer Consultation demonstrates that well-respected and highly experienced scientists believe that the most likely MOAs for several animal tumor types induced by ethylbenzene would require use of a nonlinear model to derive a unit risk figure. OEHHA should not disregard the consensus view of this distinguished group, especially because the TAC Act requires OEHHA to use "current principles, practices, and methods used by public health professionals who are experienced practitioners in the fields of epidemiology, human health effects assessment, risk assessment, and toxicity." Therefore, the Panel believes that OEHHA should also present unit risk estimates for each tumor type based on the nonlinear MOAs proposed by the Panel.

Response:
OEHHA did not consider any potential MOA sufficiently well established for the kidney, liver and lung tumor sites evaluated. Since tumor site concordance between experimental animals and humans cannot be assumed, and is seldom observed even between rodent species, the commenter’s notion of a “correct” target tissue is flawed. OEHHA has the following responses to the specific MOA and related arguments proposed in the Sapphire Group report (submitted with these comments).

Mode of action for kidney tumors
The Sapphire Group report presents a theory of an MOA for ethylbenzene induced rat kidney tumors in which tumor incidence increases are the result of increased cell division rates associated with chronic progressive nephropathy (CPN) (Hard, 2002). This is a common process in aged control rats, but it is hypothesized that ethylbenzene or its metabolites promote the incidence and/or severity of CPN. The Sapphire Group endeavors to support this hypothesis by tying the tumor response to the 1-phenylethanol metabolite and CPN. In fact the relationships between tumor incidence and CPN score (defined as CPN incidence times severity) and between exposure and CPN score are nonlinear; in other words the CPN score is not directly correlated with the kidney tumor incidence. OEHHA considers that, based on the available evidence the
Hill criteria have not been sufficiently satisfied, and that a causal relationship between kidney tumors and CPN is not established. Furthermore the high background of CPN makes interpretation of the relationship between CPN and tumor incidence difficult. For example the male rat shows a clear positive trend in kidney tumors, including significant increases at both intermediate and high doses in male rats, but there is no change in CPN severity until the highest dose. OEHHA already reviewed and discussed this mechanism in the document, and has found no basis to support a conclusion that the kidney tumors are solely due to CPN. In reaching this conclusion, OEHHA’s analysis is consistent with the views of scientists at the National Institute for Environmental Health Sciences (Seely et al., 2002). Further, as noted above, OEHHA makes no assumption as to interspecies tumor site concordance.

Mode of action for liver tumors
The Sapphire Group report presents a theory of an MOA for ethylbenzene-induced liver tumors in female mice. In this case, a “strong” positive correlation of liver tumors and the observation of eosinophilic foci is claimed, however (as shown in Figure 3 of the Sapphire Group report) the correlation in female mice is largely due to a single point, at the highest dose. There is no significant correlation \( (\mathbf{R}^{2} = 0.02) \) between liver tumors and eosinophilic foci in male mice: like the females there is a small dose-related increase in eosinophilic foci in the male mice, but no corresponding increase in the already high background tumor incidence. The pooled male and female data in rats also show no correlation between liver tumors and eosinophilic foci: foci are observed in both sexes but with no dose-response relationship, and the only liver tumors reported were in the lowest-dose males. Thus the available data are insufficient to draw a definitive conclusion regarding the implications of this supposed correlation. Further, this report uses the observation of CYP2B1 and 2B2 induction in rats to infer the induction of CYP2E1 in mice and goes on to suggest that the inferred induction of CYP2E1 in mice implies a nongenotoxic MOA for ethylbenzene-induced liver tumors. However, the inferred induction of CYP2E1 in mice could equally be associated with a genotoxic MOA related to the formation of epoxides or other reactive metabolites. It is not clear from the rationale provided why the authors think that enzyme induction leading to foci is the sole MOA operating in ethylbenzene induced liver tumors. Additionally, the Sapphire Group report postulates increased liver hyperplasia resulting from hepatic enzyme induction as part of their putative MOA for ethyl benzene carcinogenicity. However, it should be noted that Chan et al. (1998) stated “the relationship between increased liver weight and liver neoplasm incidence in the female mice is not clear”. OEHHA therefore concludes that the very limited data do not establish a lack of any genotoxic MOA for the liver cancer endpoint. Also it is uncertain what would be the quantitative nature of the dose-response relationship implied by the hypothesized non-genotoxic MOA.

Mode of action for lung tumors
The Sapphire Group report proposes an MOA for ethylbenzene-induced lung cancer in mice that is solely dependent upon the generation of cytotoxic quinone metabolites in analogy to styrene and naphthalene, which are also carcinogenic. Since ring oxidation may produce a genotoxic epoxide metabolite it is possible that more than one MOA may be operating. While OEHHA acknowledges the plausibility of quinone metabolites participating in a potential MOA for ethylbenzene-induced lung cancer in mice, it is uncertain whether this is the sole MOA operating. Moreover, the plausibility of involvement of quinone metabolites does not of itself establish the quantitative nature of the dose-response relationship: it is very plausible that a
mechanism involving oxidative DNA damage might display low-dose linearity.

Genotoxic vs. non-genotoxic MOAs
The Sapphire Group report uses the modified Hill criteria in an attempt to prove a negative, namely that ethylbenzene does not induce cancer via a genotoxic MOA. OEHHA has not claimed a genotoxic MOA for ethylbenzene but neither have we claimed that genotoxicity plays no role in ethylbenzene-induced cancer. The observation of oxidative DNA damage in vitro (Midorikawa et al., 2004) raises some interesting questions about downstream metabolites, including the analogy with benzene (a well-known genotoxic carcinogen targeting multiple sites in various species including humans). There simply are not sufficient data at present to make a definitive conclusion regarding the MOA for ethylbenzene carcinogenesis, or to rule out genotoxic activity. OEHHA considers that no convincing MOA has been established for key tumor endpoints, even in systems in vitro, that would support an alternative approach to the quantitative dose-response assessment. Assessing the dose-response relationship under alternative MOAs is not a matter of merely substituting an RfD established using uncertainty factors for the cancer potency.

Comment 4:
The Panel applauds OEHHA’s efforts to utilize physiologically based pharmacokinetic (PBPK) modeling as an alternative to a more simplistic lifetime weighted average dose in selecting a unit risk value for ethylbenzene. As explained in the attached report, however, OEHHA used incorrect parameters in its PBPK modeling for ethylbenzene. The Panel believes that OEHHA's conclusion that internal doses derived from PBPK modeling are not materially different from lifetime weighted average doses will no longer be accurate after the correct modeling parameters are utilized, and that OEHHA should use dose values derived from PBPK modeling to derive its unit risk factor for ethylbenzene.

Response:
The Sapphire Group report criticized OEHHA’s use of PBPK modeling of ethylbenzene dosimetry in rats, specifically focusing on the choice of blood:air partition coefficient and the use of a model based on studies in the Sprague-Dawley rat strain rather than the F344 rat strain that was used in the ethylbenzene cancer bioassay. Although OEHHA doubted that either of these differences would have a significant effect on the dosimetry and risk estimates, we repeated the analysis using the rat PBPK model of Dennison et al. (2003), which was based on the F344 rat. As expected, the differences observed are mainly at the high bioassay doses and had a relatively small effect on the dose response assessment. Nevertheless this alternate rat PBPK analysis is incorporated in the revised SRP review draft.

With respect to OEHHA’s use of a human PBPK model the Sapphire Group report cautions that “OEHHA should not use the Sams et al. (2004) data in PBPK modeling since simulations based on the Haddad et al. (1999, 2001) model are a better match to the experimental data. ... the average Km for the low affinity pathway of ethylbenzene metabolism is 391 µM, which converts to 41.4 mg/L rather than 40.4 mg/L as stated in Table 7. ... a better estimate for the human liver is the value of 52.9 mg/g liver from Lipscomb et al. (2003).” However, there are relatively few data available on human exposure and kinetics of ethylbenzene. The Tardif et al. (1997) study included only four adult males (70-90 kg). By using the data of Sams et al. (2004) we attempted
to include a broader range of human variability; these authors studied a total of seven subjects who included both males (4) and females (3). The low affinity Km should read 41.5 mg/L (391 &mu;M x 106.16 g/mol/1000). Regarding the human liver microsomal protein concentration, a range of values has appeared in the literature. The Lipscomb et al. (2003) value of 52.9 mg/g appears to be at the upper end of the range (e.g., Kohn and Melnick, Carcinogenesis 14:619-628 (1993), human liver micro prot 14,500 mg/L App. A).

With respect to the use of the mouse PBPK model and the pharmacokinetic data of Charest-Tardif (2006) the Sapphire Group report claims that OEHHA did not provide sufficient justification for the metabolic parameter used that provided a better fit to the data. Table 1 below provides the PBPK model predictions compared to the data of Charest –Tardif (2006). The model was set for a 0.039 kg female mouse and 4 hour exposures. The value of 25.56 mg/hr was chosen as the “better fit” since 7 of the 8 predicted Cmax and AUC values were within a factor of 2 of the observed values (Obs/pred of 0.5 to 2.0) while the original VmaxC only gave 3/8. This level of detail was considered excessive for inclusion in the OEHHA report.

Table 1. PBPK Model Predictions that Simulate the Mouse Pharmacokinetic Data of Charest-Tardif (2006)

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<th>VmacC</th>
<th>Exposure ppm</th>
<th>Cmax, mg/L</th>
<th>AUC mg min/Ld</th>
<th>Obs/pred Cmax</th>
<th>Obs/Pred AUC</th>
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**Comment 5:**
The discussion above demonstrates that OEHHA cannot satisfy its obligation under the TAC Act to use the "best available science" and to consider fully all available "mode of action" data unless OEHHA withdraws its current draft document, fully evaluates all of the relevant scientific information that is not considered in the analysis, and issues a revised unit risk document before submitting it for review by the Scientific Review Panel. The Panel notes that the VCCEP Peer Consultation process has not yet been completed, and that EPA is scheduled to release an Integrated Risk Information System document on ethylbenzene for external peer review in Spring 2008. The Panel believes that OEHHA should also seek to harmonize, to the greatest extent possible, its analytic approach with the approaches taken in these other reviews.

**Response:**
OEHHA disagrees with the assertions of inadequate consideration of scientific data in this comment. OEHHA considered the original studies cited in the VCCEP and Sapphire Group reports. Some specific additions to the document are being made in response to comments from this and other sources. OEHHA has reviewed the report of the VCCEP Peer Consultation, but disagrees with the conclusions with regard to MOA and the risk assessment choices presented therein. OEHHA does not consider it appropriate to delay consideration of ethylbenzene while USEPA completes a review process of undetermined, and probably considerable, length.
Comments of Michael D. Wang on behalf of the Western States Petroleum Association

Comment 1:
WSPA supports and agrees with the comments submitted on May 31, 2007 by the Ethylbenzene Panel of the American Chemistry Council. The carcinogenicity risk assessment performed in the Draft Report is inadequate and does not comply with the requirements of Toxic Air Contaminant Identification and Control Act.

Response:
OEHHA disagrees with the assertions of inadequate consideration of scientific data in this comment. OEHHA has reviewed the original studies cited in comments or referenced in attachments. Some specific additions to the document are being made in response to comments from this and other sources. Responses to the detailed comments of the American Chemistry Council are given in the previous section of these responses.

Comment 2:
The Draft Report does not “consider all available scientific data” since it does not consider important scientific information on the mode of action (MOA) and the unit risk factor for ethylbenzene, which has been evaluated as part of the U.S. Environmental Protection Agency (US EPA) Voluntary Children’s Chemical Evaluation Program (VCCEP Report). The VCCEP Report is the subject of a Peer Consultation by a panel of well-respected, independent scientists under the auspices of the non-profit Toxicology Excellence for Risk Assessment (TERA).

Response:
OEHHA is well aware of the discussions which are presented in the report of the VCCEP Peer Consultation. OEHHA has not referenced this data review directly in the draft document since the emphasis of our risk assessments is on primary data sources.

Comment 3
In addition, the Draft Report does not perform an adequate analysis of the MOA “using current principles, practices, and methods” as described in the US EPA (2005) Guidelines for Carcinogen Risk Assessment and as required by the regulations.

Response:
OEHHA has used appropriate and current criteria of analysis of various claimed modes of action. OEHHA is familiar with, and generally (but not entirely or uncritically) supportive of the recommendations of the US EPA (2005) Guidelines for Carcinogen Risk Assessment. This document and the associated supplemental guidance are regarded as a valuable resource and helpful as an indication of current U.S. EPA practice, but OEHHA is not required by regulations under either AB 1807 or AB 2588 to use these U.S. EPA guidelines or their predecessors without qualification.
Comment 4
As a result, the Draft Report erroneously identifies rat kidney tumors as the relevant tumor, incorrectly rejects the most likely MOA for rat kidney tumors, does not consider the most likely MOAs for the mouse lung and liver tumors, and improperly selects a linear dose-response model despite overwhelming evidence that ethylbenzene is not genotoxic.

Response:
OEHHA disagrees with the suggestion that its conclusion about proposed MOAs and their implications for risk assessment choices are incorrect. A more detailed discussion of the alternative MOAs presented here and in other comments is given in OEHHA’s response to comments from the American Chemistry Council and proposals in the Sapphire Group report concerning possible MOAs for ethylbenzene carcinogenesis. OEHHA’s overall conclusion was that there was insufficient scientific support for the proposed MOAs, and that there are several alternative interpretations of the available data. It should be noted that the criterion for accepting a proposed MOA which predicts a lower risk to public health than other plausible proposals or default assumptions, such as those implying a threshold dose-response model in carcinogenesis, is that they should be established with reasonable scientific certainty, as opposed to being hypothesized as the “most likely” MOA.

Comment 5
OEHHA should withdraw the Draft Report, fully evaluate all the relevant scientific information, and issue a revised unit risk document before submitting it for review to the Scientific Review Panel. Unless these deficiencies are addressed, risk managers will ultimately be misled into believing that the unit risk factor for ethylbenzene can be accurately estimated within a narrow range using several similar approaches to linear extrapolation. To the contrary, the weight of the scientific evidence indicates that these approaches are unlikely to accurately predict cancer risk in the low dose range of ethylbenzene. It would be unfortunate if risk managers were not informed by OEHHA of the more scientifically appropriate and likely estimates of cancer potency, which are described in the VCCEP Report and which are orders of magnitude lower than the estimates provided in the Draft Report.

Response:
OEHHA considers its current evaluation appropriate for developing a unit risk value for ethylbenzene, and intends to present the document, with additions and changes in response to specific comments received, to the Scientific Review Panel who are charged with determining its adequacy.