Responses to Public Comment on the Draft Inhalation Unit Risk Factor for Perchloroethylene

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

(May 2016)

Background

The Office of Environmental Health Hazard Assessment (OEHHA) develops potency values for carcinogenic substances that are candidate Toxic Air Contaminants (TACs) (Health and Safety Code Section 39660) or are listed under the Air Toxics Hot Spots Act (Health and Safety Code Section 44321). These values are used in the Air Resources Board's (ARB) air toxics control programs and also by other State regulatory bodies, to estimate cancer risk in humans.

On February 15, 2016, OEHHA released the draft document, *Perchloroethylene: Inhalation Cancer Unit Risk Factor, Technical Support Document for Cancer Potency Factors, Appendix B, Public Review Draft* (hereinafter referred to as "the document") to solicit public comment. The document presents an updated cancer dose-response analysis for inhalation exposure to perchloroethylene (PCE) and derives a unit risk factor (and a corresponding cancer slope factor) using methodology described in the OEHHA 2009 Air Toxics Hot Spots Technical Support Document for Cancer Potency Factors (hereinafter referred to as the "cancer TSD") and research made available since our last PCE review in 1992. Public comment was received from:

- The Center for Public Environmental Oversight (CPEO)
- The U.S. Department of Defense (DoD)
- The California Chamber of Commerce (CalChamber)
- The Halogenated Solvents Industry Alliance (HSIA)

Responses to these comments are provided below.

1. Responses to Comments Received from the Center for Public Environmental Oversight (CPEO). Comment letter signed by Mr. Lenny Siegel.

CPEO General Comment 1

"I am pleased to see that the Office of Environmental Health Hazard Assessment (OEHHA) is developing an inhalation cancer unit risk factor (URF) for perchloroethylene (tetrachloroethylene). I work with communities across the country where exposure to PCE vapors is all too common. In my own community of Mountain View, California, where I serve on the City Council, we have at least two current development projects on former dry cleaner sites where PCE was released into the subsurface.

"I do not have the expertise to comment on the technical aspects of your study. I am writing simply to say the health and property of a large number of people depend upon you doing your job carefully. Historically, the businesses that produce, use, and release chlorinated compounds have worked incessantly to weaken the exposure standards, and there is no organization with resources on the other side, representing potentially exposed communities, to balance their influence.

"So please be aware of industry's interests and influence as you complete your findings."

Response to CPEO General Comment 1

OEHHA thanks the commenter for providing contextual information regarding current exposures to PCE resulting from historical PCE use and disposal practices. With our currently proposed PCE URF update, OEHHA believes that it has used the best available scientific methodology and toxicity information, and has also taken appropriate steps to offset the remaining analytic uncertainties and data gaps, to provide a health-protective estimate for PCE's carcinogenic potency.

2. Responses to Comments Received from the U.S. Department of Defense (DoD)

DoD General Comment

"The OEHHA Perchloroethylene (PCE) Inhalation Cancer Unit Risk Factor (URF), Public Review Draft does not provide the basis or rationale for the selection of the input values used to calculate the inhalation URF. That is, given the various uncertainties it is unclear whether OEHHA is striving to develop a URF associated with the least amount of uncertainty or a URF associated with the most sensitive endpoints, especially given that the EPA Toxicological Review of Tetrachloroethylene (Perchloroethylene) (EPA 2012) developed an extensive review and analysis of the available data regarding PCE health effects and carcinogenicity, which underwent extensive public and expert peer review by the National Research Council ([NRC] 2010). OEHHA arrived at an inhalation URF approximately 23 times more stringent than the EPA (2012) value and virtually identical to the OEHHA 1992 value. To improve clarity and transparency, OEHHA should clearly state the basis for the selection of input values. In addition the document should include a comprehensive uncertainty analysis and consideration of alternate dose metrics using the OEHHA-adapted Chiu and Ginsberg (2011) model so the impact on the resulting URF associated with the OEHHA decision logic is clear to a reviewer."

Response to DoD General Comment

As noted in the introductory section of the document, OEHHA relies on the 2009 cancer TSD (OEHHA, 2009) for its methodologic basis in developing cancer potency values. The Office strives to determine potency estimates that are appropriate to protect human health. In so doing, we believe it scientifically prudent to consider and make allowances for data gaps and uncertainties in the available toxicologic information. For OEHHA's PCE cancer potency factor derivation, the basis for selection of the input values is discussed throughout the document.

For example, in Section 6, we explain our decision to base the internal dose-metric estimates on the Chiu and Ginsberg PBPK model, given that it is the most up-to-date and comprehensive model for this purpose. In Section 7, a discussion is provided of why rat mononuclear cell leukemia (MCL) was considered to be an appropriate and informative tumor type for use in human cancer risk assessment. Indeed, much of the text is devoted to explaining the various choices of our input assumptions and data. In addition, OEHHA discusses various aspects of uncertainty throughout the document.

Regarding DoD's suggestion that the Office carry out "a comprehensive uncertainty analysis," we do not believe it is necessary or desirable in this instance. In support of our position, we cite the National Academy of Sciences (NAS 2009) opinion on uncertainty analysis in risk assessment:

> "If an uncertainty analysis will not substantially influence outcomes of importance to the decision maker, resources should not be expended on a detailed uncertainty analysis..."

In our review of the current PCE toxicity database, OEHHA has identified several unresolvable uncertainties, a major one of which lies in the toxicokinetic data relating to the level of GST conjugation of PCE in humans. We refer the commenter to Chiu and Ginsberg (2011), who provided a detailed quantitative uncertainty analysis of several aspects of their PBPK model, including a close look at the sources of uncertainty/variability in the human model. In addition, US EPA (2012) explored the range of estimates that would be obtained by utilizing various dose metrics that the Office deemed to be less appropriate for carrying out the dose-response assessment. As noted in the document, OEHHA considered all of this information in its independent analysis.

Based on this comment, however, we have provided additional discussion in the document on several of the more important aspects of uncertainty in the PCE cancer potency factor derivation.

DoD Specific Comment 1

"Page 8, Section 6. The text states the Chiu and Ginsberg (2011) model was adapted by OEHHA, however the basis for this OEHHA adaptation is not provided. For transparency, provide the rationale for the adaptation of the model. Also, the text states the adapted model 'adequately' reproduced the predictions of the original Chiu and Ginsberg (2011) model, however no data or results are provided to support this claim. Recommend a quantitative measure be provided to support the claim that the adapted model is able to reproduce the predictions of the Chiu and Ginsberg (2011) model. Clarify whether the OEHHA adaptation of the model underwent a peer review or validation process."

Response to DoD Specific Comment 1

The development of the inhalation-only version of the Chiu and Ginsberg (2011) model is described in the document and the resulting model code is provided in Appendix A. The document also explains that OEHHA's model uses the relevant inhalation equations

and all of the modeling parameter values from Chiu and Ginsberg (2011), including the maximum likelihood estimates (MLEs) determined via the Markov Chain Monte Carlo calculations. Chiu and Ginsberg's model equations and input parameters were peer-reviewed and extensively validated. This represents "the basis" of the OEHHA-adapted model. Table 2 presents dose-metric estimates that were reported by Chiu and Ginsberg (2011) and were also obtained by OEHHA using its inhalation-only adaptation, at the level of significance presented in the table. Based on the concordance of the estimates, OEHHA deems its adapted model to adequately reproduce the original model results. In order to make this clearer to the reader, the Office has retitled Table 2 and added a clarification in a footnote to the table.

DoD Specific Comment 2

"Pages 9-10, Section 7. The summary of 'selected results' presented in this section does include examples of negative results in genotoxicity tests; however, given the bullet list of positive results, consideration of the uncertainty associated with the genotoxicity of PCE will improve transparency. As EPA (2012) noted, uncertainties with regard to PCE genotoxicity remain. In vivo testing has been equivocal, and although specific PCE metabolites are genotoxic, not all metabolites have been adequately tested to support definitive conclusions regarding their genotoxic potential."

Response to DoD Specific Comment 2

The primary purpose of the document is to revise the dose-response assessment and provide an updated cancer potency value for PCE. Appropriate to this objective, OEHHA streamlined its discussion of PCE as a carcinogenic hazard, including the section on genotoxicity. It is important to note that the new data available since OEHHA's last review have not altered the conclusion that PCE is a potential genotoxic carcinogen via its numerous reactive metabolites. As such, the document section on genotoxicity focuses on the positive results found in the literature. Nonetheless, we do point out several instances where equivocal test results have been obtained.

OEHHA believes that the genotoxicity discussion presented is adequate for this potency-factor update. We do not intend these sections to be comprehensive reviews of the literature. As was noted in the document, detailed genotoxicity reviews have recently been published by US EPA and IARC. Neither of these entities have changed their designations regarding the genotoxic potential of PCE and its metabolites based on the updated information.

DoD Specific Comment 3

"Page 12, Section 7, Paragraph 1. In the subsection 'Primary Studies for Dose-Response Assessment', the text states the JISA 1993 study is of high quality and suitable for the development of an inhalation potency factor, and in comparison to the NTP (1986) study, '...offers the advantage of an additional dose category for each species, as well as the use of several lower exposure concentrations' and had a lower control rate of MCL incidence. However, it appears on Page 22, that despite the advantages associated with the JISA 1993 study, the male mouse liver cancer data from the NTP (1986) study was used to calculate the URF even though the JISA (1993) study included this same endpoint. The basis/justification for including the male mouse liver data from the NTP (1993) [sic] study instead of the results from the JISA (1993) study requires a clear and transparent explanation in the text."

Response to DoD Specific Comment 3

It has been shown that different strains and substrains of rats and mice used in carcinogenicity testing programs display genetic and phenotypic variation as a result of well known mechanisms such as genetic drift. For example, Tiruppathi *et al.* (1990) and Thompson *et al.* (1991) reported that the Japanese and German substrains of the Fischer 344 (F344) rat, but not the US substrain, were deficient in dipeptidyl dipeptidase-4 activity in the kidney and liver. This enzyme has been implicated in the degradation of collagen, blood clotting, immunomodulation, and metabolism of hormonal peptides (Tiruppathi, *et al.*, 1990). While this particular enzymatic variation may not be directly relevant to PCE metabolism, it indicates that F344 rat substrains can display significantly divergent biological traits.

With regard to the mice, the genetic variation issue is accentuated since the two primary PCE rodent studies used different mouse hybrid strains, not substrains.

The two rodent cancer studies for PCE at issue here displayed variability of outcome with respect to types of tumor elevated, as well as the strength of the dose-response relationships for various tumor types. Although it unknown whether these differences resulted from genetic variability, this observation suggests that data from both the JISA (1993) and NTP (1986) provide non-redundant information for the analysis. The document noted that the JISA (1993) study had an advantage of testing animals at several lower doses than the NTP (1986) study. However, OEHHA deemed it important to also use the NTP (1986) data for the reasons listed above. The Office has supplemented the discussion in the appropriate section to make these points clearer to the reader.

DoD Specific Comment 4

"Page 12, Section 7. In the 'Relevance of MCL to Humans' section, OEHHA should supply context for the statement that the NRC expert panel did not reach consensus regarding use of the rat MCL data for human health risk assessment purposes. To improve clarity, the text should indicate the NRC expert panel was comprised of 20 individuals and that the findings of the NRC expert panel were published (169 pages), which allowed transparency regarding recommendations and discussion where the scientific evidence is unclear. The text should also note as stated in the NRC (2010) review, that the '*...majority of the members judged that the uncertainties associated with MCL...were too great to support using the data over that of hepatic or renal cancer for determining quantitative estimates of risk. These members judged that the use of the MCL data could only be justified if it is EPA 's policy to choose the most conservative unit risk when considering a range of options, but that such justification should be distinguished as a policy decision and not a scientific one.*' This recommendation was supported during the subsequent OMB review of the EPA PCE toxicity profile. Recommend including the majority finding of the NRC expert review panel with regards to selection of tumor type for quantitative assessment to improve transparency, rather than only indicating complete consensus between 20 experts regarding complicated biological processes with associated uncertainty was not achieved."

Response to DoD Specific Comment 4

OEHHA generally cites only source materials readily available to the public, to preserve transparency and accountability. In this case we limit our description of the proceedings to the information reported in the panel's summary document. The report summary (NRC 2010, at page 10) indicates the minority position as follows:

> "Other members judged that the MCL data should be used for cancer-risk estimation. Their opinions were based on the observation that reproducible, statistically significant increases in MCL in male and female rats above the background incidence of MCL were found and that MCL was the cancer end point with the highest magnitude of response. They believed that use of the most sensitive response to quantify cancer risk decreases the uncertainty associated with potential differences in metabolism and susceptibility to tetrachloroethylene among exposed populations."

OEHHA generally agrees here with the minority opinion. In addition, in the NRC report section dealing with MCL, the expert panel affirmed US EPA's statement (in justifying the use of MCL) that, "discounting a rodent neoplasm simply because it has no human counterpart is not a scientifically defensible position. Strict site concordance is not a

requirement for relevance in extrapolation of hazard potential." (see NRC, 2010, at page 77). OEHHA agrees with both US EPA and the NRC expert panel on this issue, and has previously stated this methodological principle in our cancer TSD.

Further, as noted by DoD, the NRC panel majority opinion was that US EPA should not use the MCL data "over" (i.e., rather than) the hepatic or renal data. This is because, in the 2008 US EPA draft under review, the agency proposed to use male rat MCL over other tumor types for determining the unit risk value. However, OEHHA's method is to consider the MCL dose-response data *along with* the other tumor data in mice and rats in order to define a potency value that takes account of uncertainty in the data, while also being appropriate to protect human health.

DoD Specific Comment 5

'As the 'reasonable' hypothesis presented is that mononuclear cell leukemia (MCL) is a form of Large Granular Lymphocyte Leukemia (LGLL), which is phenotypically similar to human LGLL, for completeness, the text should also indicate Thomas *et al.* (2007) noted although MCL shares some characteristics with human natural killer-LGLL (NK-LGLL), human NK-LGLL is rare, occurs primarily in the young, and are 'reported mainly from the far-east with strong implications to Epstein-Barr virus as the primary causative agent, which contrasts sharply with the high background incidence in the F344 rat. In addition, Thomas *et al.* (2007) goes on to state '*...more mechanistic information is needed for arriving at scientifically sound conclusions as to its relevance in human cancer risk assessments.*' Also, verify/clarify the finding from the Liao *et al.* (2011) study, which the text states observed similar cellular responses in samples of the two tumor cell types. The Liao *et al.* (2011) study appears to have used a Fischer F344 rat NK-cell leukemia model where RNK-16 cells from in vivo NK-cell leukemic cell line were transplanted intraperitoneally into the rats."

Response to DoD Specific Comment 5

As noted in the Response to DoD Specific Comment 4, OEHHA does not require tumor concordance between rodents and humans in order to use rodent data to estimate human dose-response factors. This was stated in the last paragraph on page 12 of the document. The additional discussion on the possible concordance between rat MCL and human leukemias and lymphomas was provided as supplementary information suggesting the possibility of concordance in this case.

Stating that human NK-LGLL occurs "primarily in the young" is a mischaracterization of Thomas *et al.* (2007). More accurately, Thomas *et al.* (2007) report that when compared

to patients with LGLL of T-cell origin, NK-LGLL "patients are younger, with a median age of 39 years..."

Regarding the Liao *et al.* (2011) paper, it indicates that both human NK-leukemia cells (*in vitro*) and F344 rat MCL tumors (*in vivo*) are susceptible to FTY720 (fingolimod) mediated apoptosis through two specific mechanisms involving suppression of MCl-1, a pro-survival protein, and the alteration of sphingolipid metabolism. This research implies that rat MCL cells and human NK-leukemia cells share fundamental oncologic traits. It is reasonable to consider the possibility these that these traits were produced by similar genetic lesions.

DoD Specific Comment 6

"Page 15, Section 7, Paragraph 2. The basis for the statement that adverse effects on blood and the immune system 'could plausibly give rise to a variety of carcinogenic response,' should be provided, as should the basis for the statement that rat MCL 'may correspond' to other types of human leukemia or lymphoma. Alternatively, the unsupported statements could be removed from the text."

Response to DoD Specific Comment 6

As noted in the response to DoD Specific Comment 5, information on the possible correspondence of rat MCL to human tumor types is provided as supplemental information, and is not the basis for the Office's use of rat MCL in the dose-response assessment. As such, we do not agree with DoD that an extensive discussion is required to support these reasonable toxicologic hypotheses.

DoD Specific Comment 7

"Page 18-19, Section 9. In the last bullet on Page 18, the text indicates the PBPK model for the GST pathway in humans involves large variability or uncertainty. In humans, the range of predicted estimates spans several orders of magnitude. In its review, EPA (2012) noted '...two local maxima were observed for the posterior nodes [sic], each of which the fit to the data was good and substantially similar. However, the model predictions corresponding to each estimate differed by 3,000-fold. It was not clear as to whether this 3,000-fold spread represented uncertainty or variability in the form of a bimodal distribution for human GSH conjugation or both.' OEHHA indicates it is reasonable to assume that some segment of the population could be efficient metabolizers and the larger of the two values is more probable, however no basis is provided for these statements. Provide the basis for these statements, especially since the use of total metabolism as the dose metric incorporates the GST pathway (and

associated uncertainty) in the derivation of each of the tissue-specific URFs used to calculate the proposed inhalation URF."

Response to DoD Specific Comment 7

Regarding the 3000-fold spread in the apparent bi-modal distribution for human GSH conjugation, the document states that Chiu and Ginsberg (2011) were unable to determine how much of the variation was due to uncertainty versus variability, but noted that it could represent variability given the known variation in GST-activity in humans. We refer DoD to Chiu and Ginsberg (2011), pages 224-225, for those authors' evaluation of the human model results. OEHHA has provided additional discussion on uncertainty in the PBPK human GSH conjugation model and its relatively small impact upon the overall results of the dose-response assessment.

DoD also requests a basis for OEHHA's statements in the document that the larger of the two posterior mode estimates for human GSH conjugation is the more probable. We point DoD to Chiu and Ginsberg (2011), page 217, where they state:

> "[T]he parameter optimization procedure revealed two distinct modes in the rate of GSH conjugation — one with 'high' GSH conjugation (the overall posterior mode) and one with 'low' GSH conjugation (a number of the alternative posterior modes). The log-likelihood for the overall posterior mode with high GSH conjugation is 38 units higher than the alternative posterior modes with low GSH conjugation..."

In addition, Table 7 of the same paper reports the post-calibration, posterior mode for the first-order rate constant in the human TCVG pathway as 5.26 L/hr, which is near the high end of the range of posterior modes reported in the same table (0.00194-5.48 L/hr).

DoD Specific Comment 8

"Page 19, Section 9, Paragraph 2. It appears only one metric was chosen for the dose-response analysis, regardless of endpoint. In EPA's assessment, multiple metrics were analyzed after consideration of the most appropriate metric for a particular endpoint. The text is unclear why total metabolism was an appropriate metric for each of the tissue-specific endpoints evaluated in the dose response analysis, especially given the uncertainty (3,000-fold) associated with incorporation of the GST-pathway in the selected PBPK model. Clarify in the text why selection of only one dose metric was considered appropriate for all of the tissue-specific endpoints given no critical analysis of other dose metrics using the OEHHA-adapted model are provided for comparison purposes."

Response to DoD Specific Comment 8

Based on the comment, OEHHA has provided additional discussion in the referenced section of the document to clarify our choice of dose metric.

DoD Specific Comment 9

"Page 21, Section 9, Bullet list. For Bullet 1, it is not clear why the tissue-specific URF or mouse liver tumors from the JISA (1993) study were not used to calculate the inhalation URF. Provide a clear basis/justification for selecting the NTP (1986) mouse liver tumor URF over the JISA (1993) mouse liver tumor URF in the calculation of the inhalation URF. For bullet 4, given the '...URF values for the mouse liver tumors and rat MCL were judged by OEHHA to be more certain in view of the qualitative and quantitative agreement between the two primary studies...' it is unclear why URFs for the brain, testicular, and renal tumors were incorporated into the calculation of the inhalation URF. The basis for including these endpoints in calculation of the inhalation URF should be clearly explained in the text."

Response to DoD Specific Comment 9

To address the comment referring to page 21, bullet 1 of the draft document, we refer the commenter to our "Response to DoD Specific Comment 3."

DoD's comment referring to page 21, bullet 4, requests clarification as to why the Office used dose-response information from the brain, testicular, and renal tumors in the male rat in the NTP (1986) study. The use of this data is based on our cancer TSD, at page 31, which states:

> "...for chemicals that induce tumors at multiple sites, the single-site approach may underestimate the true carcinogenic potential. For example, the overall assessment of cancer risk from cigarette smoking (US DHHS, 1982) or ionizing radiation (NRC, 1990) is not based on risk at one site, such as lung cancer. Instead, total cancer risk is estimated from all the sites at which agent induced tumors are observed (lung, bladder, leukemia, etc), combined."

Further, on page 11 of the document, we identify the three additional tumor types as likely to be elevated above the respective control-group (or historical control) tumor rates and also as suitable for inclusion in the dose-response evaluation.

DoD Specific Comment 10

"The OEHHA document contains no uncertainty analysis. In keeping with standard practices, recommend adding an uncertainty analysis to provide a transparent discussion of the uncertainty associated with the input parameters used to derive the inhalation URF as well as a summary of the justification for selection of the input parameter given the associated level of uncertainty."

Response to DoD Specific Comment 10

OEHHA earlier addressed the DoD General Comment that requested "a comprehensive uncertainty analysis," and in response, has added a short discussion to the document that summarizes the key aspects of uncertainty in the analysis. In response to the present comment, we refer DoD to the revised document section.

DoD Specific Comment 11

"Introduction, Page 1, Paragraph 3. Although this update is said to rely on 'recent toxicological assessments published by the US Environmental Protection Agency (US EPA, 2012a)', OEHHA's methods documentation [OEHHA's current Air Toxics Hot Spots program risk assessment guidelines (OEHHA, 2009)] is out-of-date with regard to EPA's current practice, and apparently current OEHHA practice. Two significant example issues are (1) the use of a linearized multistage model that generates a q1* rather than BMDS that generates a BMDL and (2) use of (body weight)$^{2/3}$ rather than (body weight)$^{3/4}$ for interspecies extrapolation. These differences in procedures can substantially alter the estimated cancer potency. In the next paragraph, however, the document states 'OEHHA used US EPA's Benchmark Dose Software (BMDS)', and on Page 20 (body weight) $^{3/4}$ is used."

Response to DoD Specific Comment 11

DoD mischaracterizes OEHHA's use of the US EPA IRIS toxicity assessment (US EPA 2012). We *drew upon* material from the US EPA assessment, *where appropriate.* Since US EPA's cancer dose-response methods are not entirely the same as OEHHA's, the two methodologies may sometimes diverge, and OEHHA here chooses a more health-protective approach.

DoD claims that OEHHA's guidelines are out of date, and cites two examples related to body-weight scaling and the linearized, multi-stage model. The Office points DoD to the cancer TSD Executive Summary, at page 4, in regard to these examples.

There, we state:

> "OEHHA proposes to use the Benchmark Dose method to compute potency factors rather than the more traditional linearized multistage model (LMS), although the LMS will still be used in some instances.
>
> "OEHHA will use scaling based on body weight to the ¾ power, rather than to the ⅔ power."

As was noted in the draft document, we used the latest version of US EPA's Benchmark Dose software to compute the PCE cancer potency factor, and (¾)-power body weight scaling.

DoD Specific Comment 12

"Summary of Derived Values, Page 1, first partial paragraph. '...the geometric mean of 4 dose-response values was chosen as the best estimate of carcinogenic potency.' This statement is not accurate. At best, the process takes the geometric mean of the estimated cancer potency factors, but as all of the relevant supporting documents for the models state, the cancer potency values derived are not valid within the range of the dose-response data; they are based on extrapolations therefrom. More significantly, both the q1* mentioned in this report and the BMDL used in EPA's current procedures are bounds on the best estimate of the cancer potency. Standard statistical practice when combining data is to combine the best estimates and then re-estimate the desired bound. The difference between these two practices can be quite substantial.

"Although, prior to EPA's 2005 cancer guidelines, EPA sometimes combined q1*s, this is not the best statistical practice. Since (unlike the previous methodology) the best estimate as well as the bound are presented in the IRIS documents and since the method for estimating the bound is provided in the BMD technical guidance, it is not that much more difficult with EPA's current procedures to perform the correct statistical combination of the results. Using the correct statistical procedure has the added advantage of correctly assuming that using more data provides a reduction in the uncertainty and the bound will be closer to the combined best estimate."

Response to DoD Specific Comment 12

The term "best estimate" is not statistical terminology but rather descriptive of OEHHA scientists making a balanced choice of several options for the proposed URF. As noted in the TSD, the proposed URF was obtained by taking a geometric mean of 4 candidate values. This method is supported by the cancer TSD.

Given the various unquantifiable uncertainties that affect each of the URF values, and given that OEHHA judged some of the higher potency estimates to be more uncertain, the Office decided to use a non-statistical, but reproducible rule to choose a mid-range of the available values as a "best estimate" of a URF, "adequate to protect public health."

Calculating the geometric mean of the candidate URFs is equivalent to determining the median of a log-normal distribution defined by these values. The Office does not claim that this protocol is based on any particular statistical method or assumptions. We note that the traditional method of determining "the best" URF value by choosing the most appropriate tumor type, which in many cases is also the most sensitive tumor type, is primarily a qualitative analytical procedure that also eschews more involved statistical methods.

Regarding q1*s, as noted in the response to the previous comment, we used BMDS to calculate the potency factor.

DoD Specific Comment 13

"Multi-Organ Metabolism, Page 5, Third full paragraph. 'The kidney is viewed as the main site for formation of genotoxic metabolites by β-lyase cleavage of TCVC since β-lyase activity is relatively high in this organ.' However, this discussion fails to mention that rats have a much higher rate of production of mutagenic metabolites by this process than humans. To quote one of the authors cited (Rooseboom *et al.* The Journal of Pharmacology and Experimental Therapeutics 294:762-769, 2000, bold added), 'The present study indicated that all tested Se-Cys conjugates (n5 22) indeed underwent b-elimination reactions in human renal cytosol, although the activity was lower than that in rat kidney cytosol. Between 41- and 857- fold lower intrinsic clearances (Vmax/Km) were observed in human kidney cytosol compared with rat kidney cytosol.' Given the quantitative effect of a mutagenic mode of action on cancer potency estimates, this information should be provided to the reader."

Response to DoD Specific Comment 13

The human cytosolic β-lyase activities found for selenium-cysteine (Se-cysteine) conjugates in the Rooseboom *et al.* (2000) paper and referenced in DoD's comment, were based on kidney tissue obtained from three Danish men, all of whom died of cancer, and two of whom were elderly (77 and 78 years). This represents a very narrow sample of the human population and likely underestimates the true variation in human kidney β-lyase activity. Further, this study used the selenium analogues of cysteine conjugates and did not look specifically at TCVC as a cytosolic β-lyase substrate. An

additional caveat on this data is that no information is provided in the paper as to whether these individuals were undergoing chemotherapy or other medical interventions that may have altered their kidney metabolism prior to death.

Green *et al.* (1990) measured kidney cytosolic β-lyase activities for TCVC in rats and 7 human kidney samples indicating a smaller ratio between rat and human intrinsic clearance of about 25. Again, the human sample size is small, and the samples in this study were obtained from cancer patients or individuals suffering from kidney failure, which creates uncertainty regarding data quality.

However, Lash and Parker (2001) noted that: (1) cytosolic protein studies do not provide data on the levels of mitochondrial β-lyase activity, which could play an important part in this metabolic pathway, and (2) renal cytosolic β-lyases are inducible in rat by preexposure to PCE, which indicates that they could be inducible in humans. This could be an important factor increasing β-lyase activity in chronically exposed humans.

OEHHA also points out that potentially genotoxic dichloroketene and TCVC sulfoxides can be formed by alternative pathways involving TCVC oxidation in both kidney and liver (and possibly other tissues as well).

Given these and other uncertainties regarding the full sequence of events in the GST-conjugation pathway, it would be somewhat misleading to present the reader with partial information on the difference between the intrinsic clearance of Se-cysteine conjugates in humans and rats.

DoD Specific Comment 14

"Pharmacokinetic Model, Page 7. 'Table 2 shows a summary of model predictions for several types of dose-metric, as reported by Chiu and Ginsberg (2011).' Since this document did not use the Chiu and Ginsberg model, but rather a simplified version thereof, it would be more useful to see the same information for the model actually used in this analysis. Repeating information that is publically available does not excuse the analyst using a simplified version of the model from presenting the effects of the modifications on the choice of dose metric. The results of the unmodified model are not relevant to this analysis."

Response to DoD Specific Comment 14

Please refer to OEHHA's "Response to DoD Specific Comment 1."

DoD Specific Comment 15

"Pharmacokinetic Model, Page 8, Paragraph 1. 'In spite of the unresolved issues related to PCE's GST metabolism, OEHHA considers the Chiu and Ginsberg model to be the best available methodology for estimating dose metrics in the dose-response assessment.' If the best model produces an up to 3000-fold range for human exposures, it is unclear why OEHHA chose to reanalyze the data with 'a simplified, deterministic version of the model' with a 'pared-down version of the code'. Since the results of the best model are available, they should be used."

Response to DoD Specific Comment 15

Our use of the inhalation-only components of the Chiu and Ginsberg (2011) model, which was clearly described in the document, is not a reanalysis of the data. OEHHA extracted the requisite equations from the full model and utilized Chiu and Ginsberg's maximum likelihood estimates (MLEs) that were calculated by the authors using the Markov Chain Monte Carlo sampling technique. Once these estimates are derived, they can be used to run the model in deterministic mode. The only simplification that OEHHA made was to extract the intact inhalation-only code components from the full model for our more limited objectives of carrying out inhalation dose calculations. Thus OEHHA did use the best model available.

DoD Specific Comment 16

"Genotoxicity and Carcinogenicity, Page 9, Paragraph 1. OEHHA conflates genotoxicity and mutagenicity, and defines neither. As EPA's 2005 supplemental guidance describes procedures for a mutagenic mode of action, it is critical that OEHHA define and differentiate mutagenicity from genotoxicity."

Response to DoD Specific Comment 16

OEHHA methodology as described in the cancer TSD, does not depend upon making a sharp distinction between genotoxicity and mutagenicity.

The cancer TSD, at page 18, states:

> "Genetic damage in exposed organisms includes both gene mutations (point or frameshift), and larger scale effects such as deletions, gene amplification, sister-chromatid exchanges, translocations and loss or duplication of segments or whole chromosomes. These genetic effects of chemical exposures are deleterious in their own right. In addition, <u>since carcinogenesis results from</u>

> somatic mutations and similar genetic alterations, agents that cause genetic damage generally have carcinogenic potential." (emphasis added)

Later sections of the cancer TSD define OEHHA's method of adjusting carcinogenic potency to account for potentially higher sensitivity in early life stages. The cancer TSD, at page 68, explains that OEHHA's methodology for defining Age-Dependent Adjustment Factors (ADAFs) differs from US EPA's method as follows :

> "U.S. EPA is recommending the ADAFs described above only for mutagenic carcinogens, because the data for non-mutagenic carcinogens were considered to be too limited and the modes of action too diverse to use this as a category for which a general default adjustment factor approach can be applied. OEHHA considers this approach to be insufficiently health protective. There is no obvious reason to suppose that the toxicokinetics of non-mutagens would be systematically different from those of mutagens. It would also be inappropriate to assume by default that non-mutagenic carcinogens are assumed to need a toxicodynamic correction factor of 1."

Therefore, contrary to DoD's assertion, it is not critical to our dose-response analysis that we differentiate between genotoxic and mutagenic carcinogens.

DoD Specific Comment 17

"Dose-Response Assessment, Pages 18-19. The conclusion at the top of the page 'there are insufficient grounds to evaluate PCE as primarily a non-genotoxic carcinogen using a non-linear model.' has morphed to (by the bottom of the next page), 'Since PCE is considered to be a genotoxic carcinogen'. If OEHHA is following EPA's 2005 cancer guidelines, the appropriate explanation would be that, since the mode of action is not known, the default assumption of low-dose linearity was used. Otherwise, a mode of action analysis, per EPA's 2005 guidelines, should be provided. The only modes of action described in the document are a2u-globulin nephropathy in the male rat, and PPARa activation for mouse liver tumors. No formal mode-of-action analysis is presented for any mode of action, and a 'genotoxic carcinogen' is not described or defined.

"The document should be consistent as to whether PCE is considered to have a mutagenic mode of action, a genotoxic mode of action, or an unknown mode of action. Since the mode of action is used to justify the choice of dose-response model, the observed inconsistency within the document regarding the mode of action must be rectified."

Response to DoD Specific Comment 17

The bottom of page 15 of the document states:

> "PCE's carcinogenic mode of action (MOA) likely involves the genotoxicity of one or more of its oxidative- or GST-pathway metabolites, although the precise mechanisms are unknown."

More accurately, we should have said, "mode(s) of action," and we have corrected this in the document draft. Regarding the issues of genotoxicity, non-genotoxicity, and mutagenicity, and their implications for the dose-response analysis, OEHHA's methodology diverges from that of US EPA (2005) on this point. (Also see the response to the previous comment.) Thus, we emphasize that we are not following US EPA's 2005 cancer guidelines in this respect.

Moreover, the Office notes that while the document identifies various PCE metabolites as potential genotoxicants *and thus as potential carcinogens*, we neither require a finding of mutagenicity nor a "formal mode-of-action analysis" to support our choice of dose metric and our choice of the dose-response model with which to fit the data. OEHHA currently uses the US EPA BMDS implementation of the multi-stage cancer model for dose-response modeling of chemicals identified as potential carcinogens. Further, OEHHA also assumes low-dose linearity of the dose-response function for all potential carcinogens, unless convincing information is available for a carcinogen that would indicate otherwise. This is true for chemicals that OEHHA identifies as genotoxic, or as mutagenic, or even for substances that may act primarily as non-genotoxic carcinogens.

DoD Specific Comment 18

"Dose-Response Assessment, Page 20, 1st Full Paragraph. 'When multiplied by the BMR, the reciprocal of the BMDL gives a unit risk factor that is generally close in value to, and is used in place of (q1*).' This statement requires a citation since it is only true if the lower bound on dose is 'generally close in value to' the upper bound on risk, an assertion that is unlikely. The accurate statement is that the BMR divided by the BMDL provides the slope of the linear extrapolation from the BMDL to the origin. This is rarely, if ever, equivalent to the q1* generated by the 'traditional [linearized] multistage model' cited on the previous page. Problems with the linearized multistage model, e.g., that for some data sets the q1* generated was the upper-bound of the x-axis, are one of the reasons for the use of the benchmark dose approach.

"The linear extrapolations from the linearized multistage model that generates the q1* and the extrapolation from the BMDL from a BMR are not equivalent, as suggested in the quoted sentence. In particular, the BMDS allows the user to choose the BMDR and selection of different BMDRs for the same data generate significantly different estimates (as evidenced by EPA's current draft of RDX with results from various BMRs for the same data). The only equivalence to the BMR divided by the BMDL to the q1* is that both procedures have been used by EPA to estimate cancer potency. The two procedures, however, would not be expected to provide the same estimate of cancer potency."

Response to DoD Specific Comment 18

First, as we noted in the document, OEHHA used the US EPA BMDS implementation of the multi-stage cancer model to fit the dose-response data. With regard to DoD's detailed criticism of OEHHA's comparison of the BMDS multi-stage cancer model (which calculates a BMDL) and the linearized multistage model (which calculates a q1* value), OEHHA is observing the fact that in general values calculated by these two different methods are similar, not arguing about their statistical equivalence. In any event this will not affect the outcome of OEHHA's dose-response calculations or any other substantive aspect of the analysis presented in the TSD. Thus we acknowledge the comment but disagree with it.

DoD Specific Comment 19

"Dose-Response Assessment, Page 20, Third Full Paragraph. '...the combined cancer potency was also estimated for these groups using the multi-site tumor module provided in BMDS.' Based on EPA's 'Technical Background for MS Combo Program', OEHHA may have used this procedure improperly. The background document states that the result of this program, 'are valid only when the tumors are assumed to be independent of one another (conditional on dose level).' OEHHA assumes the same metric is valid for all tumor sites, may be assuming (per comment above, it is not clear) that PCE is a 'genotoxic carcinogen' for all sites, and dismisses organ-specific modes of action for liver and kidney tumors. Thus, it would appear that OEHHA is assuming that the tumors have similar modes of action. If this is an accurate interpretation of the text, the BMDS combo program cannot be used to combine the tumor sites. If OEHHA believes the tumors have different modes of action, the key events that differentiate those modes of action should be clearly stated. Otherwise, the data should be reanalyzed using an appropriate method, e.g., all tumor-bearing animals."

Response to DoD Specific Comment 19

DoD states that the BMDS "MS_combo" program cannot be used to combine tumor site risks unless the tumors are assumed to be independent of one another (conditional on dose level). In using the MS_combo module of BMDS, OEHHA assumes that the various tumor types are largely independent.

OEHHA makes no particular assumptions about the various modes of action operating to create these tumors. In the document, the Office states that PCE's carcinogenicity "likely involves" genotoxicity of its metabolites, but this is only one of many components of a complete mode of action. The expectation that risk of tumorigenesis at different sites contributes independently to the overall cancer risk is a common default assumption (related to the usual assumption of additivity for risks from exposure to different carcinogens), supported by arguments in US EPA and OEHHA cancer risk assessment guidelines and generally supported by experimental observations. There is no implicit assumption that cancers at the different sites are all caused by the same mechanism. In this case there are no specific data indicating that the tumors would be strongly associated statistically or biologically.

DoD Specific Comment 20

Page 22, Table 5. Table 5 is not labeled.

Response to DoD Specific Comment 20

OEHHA has added a label to the table noted in the comment.

3. Responses to Comments Received from the California Chamber of Commerce (CalChamber)

CalChamber General Comment 1

"Overall we question the process being undertaken for the OEHHA PCE potency value update. The U.S. EPA recently (in 2012) updated the Integrated Risk Information System (IRIS) dataset including the full breadth of available science on PCE generating health-protective toxicity information applicable to the entire nation. The outcome of the U.S. EPA's multi-stakeholder, multi-million dollar IRIS update effort (including documented review and responses to interagency reviewers from scientists from other non-EPA federal agencies, White House offices, and independent scientists external to EPA, as well as the public) was publication of a revised PCE inhalation cancer unit risk factor of 2.6E-07 per µg/m^3, backed by a 1,077-page Toxicological Review. The U.S. EPA affirmed (in June 2013) in OSWER Directive 9285.7-86 that IRIS serves as the 'gold standard' for selection of nationwide U.S. EPA Regional Screening Levels (RSL). It seems that instead of departing from current human health risk assessment best practices and unnecessarily revisiting the work only recently performed through a 'gold standard' process, OEHHA could instead adopt the U.S. EPA values without excessive revision and reconsideration, and this approach would both protect human health and thoughtfully steward California’s limited resources."

Response to CalChamber General Comment 1

OEHHA has independent responsibility under California law to develop cancer potency values for protecting the health of people living in California. In May 2009, the Office published its most recent cancer assessment guidance document, "Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures," (the "cancer TSD") pursuant to its responsibilities under California's Air Toxics "Hot Spots" (ATHS) Information and Assessment Act. The dose-response methodology presented in the cancer TSD is based upon the latest scientific knowledge as of the date of its preparation, and was independently reviewed by the Scientific Review Panel on Toxic Air Contaminants (SRP), established by the California Health and Safety Code, Section 39670.

In developing the cancer TSD, OEHHA scientists critically assessed US EPA's cancer risk assessment methods as documented in their 2005 guidelines (US EPA, 2005). OEHHA agrees with various aspects of US EPA's methods, and thus portions of the cancer TSD are consistent with US EPA guidance. However, OEHHA's methodology is

not the same as US EPA's, and where it differs, it tends to be more health-protective. The commenter may refer to the cancer TSD for additional details. It should be noted that federal air pollution law does not preclude California from independently defining health criteria that are more protective (i.e., more restrictive) than those defined by US EPA.

In updating PCE's cancer potency factors, OEHHA relied primarily on our cancer TSD and other previously developed OEHHA guidance, where relevant. Like US EPA, we used "the full breadth of available science on PCE generating health-protective toxicity information..." We have used the best available risk assessment methodology and toxicity data in estimating PCE's cancer potency factors for California, and have provided an adequate level of safety in consideration of the numerous irreducible uncertainties in the available toxicity data.

Finally, the commenter refers to OSWER Directive 9285.7-86, which is a US EPA (2013) document entitled, "Tier 3 Toxicity Value White Paper." In it, US EPA notes that OEHHA's toxicity values are credible because they "rely on best available science," and, "have undergone a high degree of scrutiny and peer review..." We agree with US EPA on this point.

CalChamber General Comment 2

"Similarly, OEHHA appears to be engaged in an exercise of 'raising the bar,' presumably to ensure continually more stringent evaluation of PCE, but fails to cite recent emissions data that show PCE is no longer the health concern for California residents that it may have been in the past. OEHHA should acknowledge that PCE is both less toxic than originally thought, and is hardly detectable in California air as of 2013. With these considerations in mind, a more appropriate focus for scientific consideration and public funding should be pollutants that may pose a greater risk than PCE."

Response to CalChamber General Comment 2

Per California law, OEHHA develops quantitative estimates of cancer potency for chemicals that have been defined as California TACs, and the Office used its cancer TSD and other recent scientific information to do so. OEHHA's methods are not exactly the same as US EPA's, and in some cases utilize more health-protective assumptions in the face of uncertain toxicity information. Thus, the Office may derive higher potency values than would US EPA, even while relying on similar toxicity information and modeling methods.

On CalChamber's second point: The draft PCE cancer potency factor update provides a description of the method by which the Office carried out its dose-response assessment to derive these values. With respect to PCE's carcinogenic effects, our analysis does not indicate that it is less toxic than originally thought. We agree with CalChamber that ambient air concentrations of PCE in California have been diminishing over time, and note that this is a result of successful state regulatory programs designed to achieve this goal. Nonetheless, PCE remains a California TAC, and the Office has statutory responsibility to develop and update the cancer potency factor for PCE as necessary.

CalChamber General Comment 3

"We question the scientific rationale for selection of data from the NTP (1986) study as the basis for calculation of the cancer potency factor in this update, when that same data was rejected previously by both OEHHA (1992) and more recently by the U.S. EPA (2012) as inadequate, of insufficient applicability to humans and, additionally, of insufficient quality for that purpose. The reasons for OEHHA to select the cancer endpoint from the 1986 study in 2016 when that data was rejected in 1992 are not transparent and should be fully explained. The implication of inclusion of the flawed 1986 NTP data mathematically allows OEHHA to calculate a more potent PCE toxicity value, as demonstrated on page 22 of the Public Review Draft. However, this approach is not consistent with best practice in risk assessment. Reliance on NTP (1986) despite previous detailed assessments rejecting same should be revisited, should OEHHA elect to pursue development of a cancer potency factor instead of adopting the IRIS PCE inhalation potency value. At the very least, Peer Review Panel charge questions should include, 'Is a combined cancer site' approach using the 1986 NTP study consistent with sound science? If so, why was this not the approach used by OEHHA in 1992 when it first assessed PCE's cancer potency? Why was this approach not taken by the U.S. EPA in the recent IRIS update for PCE?"

Response to CalChamber General Comment 3

OEHHA's 1992 dose-response analysis did utilize the NTP (1986) study data. The summary section of OEHHA (1992), at page 1-4, states that the data from both rats and mice from the NTP 1986 studies were used to derive the cancer potency estimates. The recommendation section, at page 5-33 of the same document, states that the "carcinogenic risk potency range is taken from the 1986 NTP rat and mouse studies."

However, OEHHA's 1992 analysis, which was based upon pre-2009 guidance, chose a more limited set of tumor data from the NTP (1986) study than was used in the update.

The 1992 evaluation evaluated mouse liver tumors and rat mononuclear cell leukemia, whereas the update included other tumor types for both species.

The inclusion of additional tumor types in the update is consistent with OEHHA's 2009 cancer TSD which uses a fuller range of tumor data and statistical methods of risk summation when increased tumors are observed at multiple sites in the exposed animals. According to the cancer TSD, at page 31:

> "For most carcinogens, the selection of the most sensitive site in the animal studies is recognized as providing a risk estimate which is appropriate to protect human health. However, for chemicals that induce tumors at multiple sites, the single-site approach may underestimate the true carcinogenic potential. [...] Instead, total cancer risk is estimated from all the sites at which agent induced tumors are observed (lung, bladder, leukemia, etc.), combined."

> "For carcinogens that induce tumors at multiple sites and/or with different cell types in a particular species and sex, OEHHA derives the animal cancer potency by probabilistically summing the potencies from the different sites and/or cell types."

Additionally, US EPA did not reject the NTP (1986) data as inadequate. For example, Section 5.3.1 of US EPA's IRIS Toxicological Review for PCE (US EPA, 2012), which describes the choice of data for dose-response calculations, states:

> "[S]everal chronic exposure studies in rats and mice include an oral gavage study in mice and female rats by the National Cancer Institute (NCI, 1977) and two inhalation studies in mice and rats (JISA, 1993; NTP, 1986). These studies established that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, results in increased incidence of tumors. Mouse liver tumors (hepatocellular adenomas and carcinomas) and rat mononuclear cell leukemia (MCL) were reported in both sexes in two lifetime inhalation bioassays employing different rodent strains, and mouse liver tumors were also reported in both sexes in an oral bioassay (NCI, 1977). Tumors reported in a single inhalation bioassay include kidney and testicular interstitial cell tumors in male F344 rats (NTP, 1986), brain gliomas in male and female F344 rats (NTP, 1986), and hemangiomas or hemangiosarcomas in male Crj:BDF1 mice (JISA, 1993)."

> "This analysis considers all three bioassays but focuses primarily on the JISA (1993) study results."

> "The NTP (1986) study was utilized for modeling the increased incidence in renal cancers, brain cancers, and testicular tumors with treatment reported only in this bioassay."

Further, as indicated in Table 5-18 of the IRIS Toxicological Review, US EPA calculated potency values for a variety of mouse and rat tumors using both NTP (1986) and JISA (1993) data sets. Thus, contrary to the commenter's assertion, it appears that US EPA found the NTP (1986) study to be sufficient quality to be considered in its quantitative dose-response evaluation.

Finally, CalChamber refers to the NTP (1986) data as "flawed" but has not provided any justification for this characterization.

CalChamber General Comment 4

"The OEHHA announcement for this review states, 'After the close of the public comment period, the documents will be revised as appropriate by OEHHA, and peer reviewed in 2016 by the State's Scientific Review Panel (SRP) on Toxic Air Contaminants.' If OEHHA elects to pursue independent development of cancer potency factors instead of adoption of the U.S. EPA cancer potency value as suggested, we urge OEHHA to consider an independent third party peer review separately from activities of the State's internal SRP review to increase the breadth and depth of expertise engaged in the process. In addition, release (in advance of any peer review activities) of draft charge questions before the peer review panel work begins would allow public input on the charge questions and encourage a robust review that addresses the issues of OEHHA as well as the broader stakeholder community.

"In summary, recognizing (a) that California faces limited resources, (b) that PCE is both less toxic than previously considered and no longer the air contaminant that it once was, (c) that the U.S. EPA recently thoroughly reviewed PCE science and developed cancer potency factors protective of health across the nation, and (d) that both OEHHA in 1992 and the U.S. EPA in 2012 rejected the data that is the basis for the current proposed draft PCE toxicity value, we encourage OEHHA to reevaluate any benefit to developing this additionally stringent potency value for PCE. Adoption of the IRIS value instead---a value that is founded on a very rigorous scientific process---would allow the State to focus resources and scientific attention on Toxic Air Contaminants of potentially greater concern to citizens of California."

Response to CalChamber General Comment 4

The Scientific Review Panel on Toxic Air Contaminants (SRP) is composed of highly qualified scientists who are professionally active or engaged in the conduct of scientific research, per California Health and Safety Code, Section 39670. The SRP review process thus constitutes the "independent third party peer review" process as called for by the commenter.

Regarding the restatement of comments in the summary paragraph, please refer to the responses to General Comments 1, 2, and 3.

CalChamber Specific Comment 1

"Page 1 of the Public Review Draft notes, 'OEHHA develops potency values for carcinogenic substances that are candidate Toxic Air Contaminants (TACs) or are listed under the Air Toxics Hot Spots Act. These values are used in the Air Resources Board's (ARB's) air toxics control programs and also by other State regulatory bodies, to estimate cancer risk in humans.' The draft fails to note specific examples of where the OEHHA potency value is used, such as in the Multiple Air Toxics Exposure Study (MATES IV) or in California's RWQCB Effects Screening Levels (ESLs). These points are important because the result of OEHHA's proposal to increase the PCE cancer potency value will have ramifications for these programs. Additionally, increasing the PCE cancer potency value as proposed will send a confusing message to the citizens of California because of inconsistency with the message delivered in May 2015 that PCE is no longer the public health concern it once was (e.g., SCAQMD 2015). In addition, cleanups under RWQCB will be evaluated to a more stringent PCE ESL standard and taxpayers will bear the burden of updating that ESL guidance to keep up with OEHHA‟s 'new,' more stringent proposed PCE cancer potency value."

Response to CalChamber Specific Comment 1

The primary purpose of the document is to revise the dose-response assessment and derive updated cancer potency values for PCE based upon new toxicologic information and OEHHA's most recent cancer assessment methodology. The document is not intended to provide a detailed discussion of how cancer potency values are used along with population exposure information to manage health risk in California's various environmental health protection programs and other health risk reduction activities. The commenter appears to confuse the concept of a chemical's cancer potency, which is derived through a risk assessment process, and that chemical's use and prevalence in the environment, which is addressed by regulatory agencies through a risk management process. In addition, we note that the updated PCE cancer potency factor is nearly unchanged from the 1992 value.

CalChamber Specific Comment 2

"Page 2, Section 3 'Major Sources and Uses' cites outdated (2004) facts and figures related to PCE production and demand: the first six lines of Section 3 should be updated to use 2015 figures, or the most recent data available. In addition, the final sentence of Section 3 unnecessarily cites outdated (2010) figures where more current

data are available. OEHHA should acknowledge and cite the MATES IV study conducted in 2012-2013, with a final report published in May 2015 (SCAQMD 2015). That study observed, 'PCE shows a continuing reduction in levels, likely a result of a number of air quality rules leading to the gradual phase-out of its use as an industrial and dry cleaning solvent' in California.

"Specifically, SCAQMD (2015) noted, 'Concentrations of PCE… have become so low such that the typical ambient concentrations are often below the detection limits of the measurements.' The actual measured annual average concentration of PCE in 2012-2013 was 0.03 ppb in the basin studied and SCAQMD found a 37% reduction in PCE between 2009 and 2012. Any update to the public should include the most recently available data so taxpayers are properly informed as to the potential magnitude of a PCE health risk. If OEHHA is not able [to] update Section 3 to use current 2015-2016 figures, the draft should clearly state that 2004 and 2010 data are the most recent available for this effort and thus remain appropriate. Additionally, a summary of MATES IV and findings reported in SCAQMD 2015 (or the most recent statewide report) should be included and explained in context to the PCE update."

Response to CalChamber Specific Comment 2

As noted in the previous response, the primary purpose of the document is to revise the dose-response assessment and derive updated cancer potency values for PCE based upon new toxicologic information and OEHHA's most recent cancer assessment methodology. The document is not intended to provide a detailed PCE emissions inventory analysis, nor is its purpose to carry out an exposure assessment for sites located in the South Coast Air Quality Management District (SCAQMD), such as sites covered in the MATES-IV study.

TAC emissions inventories are developed by the Air Resources Board (ARB) in cooperation with California's local air quality management districts. The PCE emissions data for 2010, provided in Section 3 of the document, represents the most recent statewide estimate published by ARB. The commenter also asserts that Dow Chemical Company's 2008 report of U.S. demand for PCE in 2004 is "outdated," but does not provide an alternative estimate or updated source of information to show that the value is, in fact, outdated. Although the estimate was for 2004 and current demand may be lower, the Dow estimate may still be reasonably representative of current demand, and at a minimum, provides the reader with context on the use of PCE in recent history.

CalChamber Specific Comment 3

"Page 2, Section 5 'National and International Hazard Evaluations' includes only select information resulting in an incomplete representation of available information. A comprehensive discussion of the U.S. EPA (2012) IRIS toxicological profile process (including the NRC 2010 peer review, and other independent reviews) is distinctly missing. As an example of how this selective inclusion of information can be misleading, the Section 5 text might lead the reader to think that specific animal cancers are linked to PCE ingestion. OEHHA wrote, 'The NTP report noted that PCE exposure produced tumors in multiple tissue types of both sexes of mice and rats, by ingestion and/or inhalation. The tumor types cited by NTP were: mononuclear-cell leukemia in rats, tubular-cell kidney tumors in male rats and liver tumors in mice.' However, in actuality, the U.S. EPA (2012) found that only inhalation PCE studies were relevant, as the single ingestion (gavage) study was determined to be 'inconclusive with respect to carcinogenicity due to a high incidence of respiratory disease in all animals and shortened survival in PCE-exposed animals.' U.S. EPA (2012) peer reviewers noted (and the IRIS Toxicological Review reflects) that because the available oral gavage cancer bioassay was inconclusive due to respiratory infection in all groups, and therefore it cannot be concluded based on that ingestion study that PCE caused tubular cell kidney tumors in male rats. In addition, U.S. EPA (2012) summarize rodent studies of PCE addressing renal α2u-globulin accumulation that support the well-known toxicology concept that this type of kidney damage is a phenomenon that occurs only in male rats and that is irrelevant to humans (see Table 4-53 of the IRIS Toxicological Review and related text).

"Text appears to be selectively citing out of context and without relevant technical details. The purpose of this selectivity seems oriented at making the case that PCE causes all manner of cancers, a point central to development of the conclusion on page 22 and which is a necessity to support the approach of taking the geometric mean across cancer endpoints and across studies in multiple species. A more balanced approach is recommended, one that would be more useful to the public in Section 5. OEHHA should select a singular cancer end point and key study upon which to focus (i.e., liver cancer from JISA 1993, or alternate key study and endpoint); data for this endpoint should be summarized with consideration to consensus across national and international assessments so as not to lose the reader in contentious details that combine rats with mice, types of tumors, and multiple studies in a geometric mean method that is not used in other cancer potency derivation methods for human health risk assessment."

Response to CalChamber Specific Comment 3

The commenter asks for a "comprehensive discussion of the US EPA (2012) IRIS toxicological profile process (including the NRC 2010 peer review, and other independent reviews)." The purpose and scope of the document is clearly described in the document introduction. A comprehensive discussion of the U.S. EPA (2012) toxicological profile is not part of the purpose or scope of the document.

With regard to the document statement that, "The NTP report noted that PCE exposure produced tumors in multiple tissue types of both sexes of mice and rats, by ingestion and/or inhalation. The tumor types cited by NTP were: mononuclear-cell leukemia in rats, tubular-cell kidney tumors in male rats and liver tumors in mice," we agree that the sentences at issue should be edited to convey the NTP determinations more accurately and have made the appropriate edits to the document.

The commenter also notes that US EPA determined that the data for rats in the 1977 National Cancer Institute (NCI, 1977) oral gavage study was not useful for use in its inhalation dose-response analysis due to problems with respiratory disease and shortened survival of the exposed animals. OEHHA does not rely on the NCI (1977) oral study for its quantitative dose-response analysis, but uses appropriate information from the study as qualitative supplemental information. OEHHA's analysis of kidney tumors in rats is based on the NTP (1986) inhalation study.

CalChamber also notes that the US EPA (2012) toxicological review includes a discussion of renal α2u-globulin accumulation. OEHHA's document for PCE also includes a discussion of this issue and why it is unlikely to be relevant in the case of rat kidney tumors induced by PCE exposure.

CalChamber also disagrees with OEHHA's use of tumor data from multiple studies, species, and multiple tissue types to inform the choice of a cancer potency value for PCE. CalChamber states that 1) OEHHA should not use a geometric mean of multiple dose-response estimates and 2) OEHHA should select a single cancer end point from a single study. OEHHA refers the commenter to our responses to CalChamber Specific Comments 6, 7, and 8, which are concerned with the same issue.

CalChamber Specific Comment 4

"On page 22, OEHHA quantitatively relies upon the NTP (1986) rat leukemia data, ignoring the Science Advisory Board of the U.S. EPA's observation that although leukemias were observed in the PCE-exposed rats in the NTP (1986) inhalation bioassay, control rats in another 1986 NTP bioassay (for methylene chloride, captured

in the IRIS Toxicological Review for that substance) showed the same incidence of leukemias as the PCE-exposed animals. The NTP (1986) rat leukemia data were specifically deemed questionable, and after extensive peer review detailed in the 2010 NRC report, were ultimately not incorporated into the U.S. EPA (2012) IRIS potency factor for PCE. OEHHA should acknowledge that exclusion of this data from use in development of a potency factor is both credible and appropriate considering the rate of spontaneous leukemias in the 1986 NTP studies and in recognition of the robust consideration already given the data. If OEHHA does not adopt the U.S. EPA PCE potency value and pursues an independent revision to the PCE potency factor, then additionally, OEHHA should add discussion of this weakness in the data to text on page 15, delete the NTP (1986) rat leukemia data from Tables 4, 5, and 6, and delete the weighting for this endpoint from any quantitative 'combined site' modeling. This will impact the NTP male rat 'multiple tumor' row on the page 22 table, and will change the largest (most conservative) URF that OEHHA has calculated for the NTP 'combined site' input to the geometric mean of 6.06E-06 per $\mu g/m^3$. Inappropriately including the NTP (1986) leukemia data results in miscalculation of the PCE potency factor resulting in an excessively conservative number which, consequently, generates a value inconsistent with what the U.S. EPA (2012) established to be reliable and appropriate after extensive public comment and multi-stakeholder, external peer review."

Response to CalChamber Specific Comment 4

We refer the commenter to the detailed discussion in the document supporting the use of rat MCL in the dose-response assessment. In addition, also see OEHHA's responses to DoD Specific Comments 4 and 5, which provide additional discussion of the rat MCL issue.

CalChamber mischaracterizes OEHHA's technical approach when it says that the Office "relies upon the NTP (1986) rat leukemia data [...]" Instead, OEHHA's method is to consider the MCL dose-response data from both the JISA (1993) and NTP (1986) studies, *along with* the other tumor data in mice and rats in order to define a potency value that uses a range of the high-quality dose-response information, takes account of uncertainty in the data, and is "appropriate to protect human health," per our cancer TSD.

Finally, regarding use of the NTP (1986) rat MCL data: Please see the OEHHA response to DoD Specific Comment 3. Additional discussion on this topic is provided in the response to CCC Specific Comment 11.

CalChamber Specific Comment 5

"In Tables 5-7 and mathematically in the potency factor calculated for PCE on page 22, OEHHA includes another irrelevant and poor quality cancer endpoint from the NTP (1986) data set. As noted previously in Specific Comment 3, U.S. EPA (2012) explained the poor human relevance of the kidney tumors in male rats found in the NTP (1986) bioassay. CDC/NIOSH and OSHA agreed with the U.S. EPA, the EPA Science Advisory Board and NRC (2010) that these tumors may not be good predictors of human risk; no other modern U.S. risk assessment uses the NTP (1986) rat kidney tumor data. If OEHHA does not adopt the U.S. EPA PCE potency value and pursues an independent revision to the PCE potency factor, then at a minimum, OEHHA should strike male rat 'renal adenoma or carcinoma' data from all tables and text, including removing it from Table 4, Table 5, and the Table 6 row for individual modeling endpoints, as well as from the 'combined site' dataset, and then remodel the results. Use of the rat kidney tumor data, as with the NTP (1986) rat leukemias, is in stark contrast to the position of every other regulatory body that has had expert peer review and critical toxicology input on the topic of relying quantitatively on this endpoint from the NTP (1986) study, which OEHHA did not rely upon in 1992. A Peer Review Panel charge question should be, 'Should OEHHA include renal α2u-globulin nephropathy-influenced kidney cancer endpoints in the quantitative potency factor, even though OSHA, CDC/NIOSH and U.S. EPA all acknowledge this male rat phenomenon is not relevant to humans?' "

Response to CalChamber Specific Comment 5

OEHHA restates part of its response to CalChamber General Comment 3, as follows:

CalChamber mischaracterizes US EPA's assessment and use of the NTP (1986) study data. US EPA did not reject the NTP (1986) data as inadequate. For example, Section 5.3.1 of US EPA's IRIS Toxicological Review for PCE (US EPA, 2012), which describes the choice of data for dose-response calculations, states:

> "Several chronic exposure studies in rats and mice include an oral gavage study in mice and female rats by the National Cancer Institute (NCI, 1977) and two inhalation studies in mice and rats (JISA, 1993; NTP, 1986). These studies established that the administration of tetrachloroethylene, either by ingestion or by inhalation to sexually mature rats and mice, results in increased incidence of tumors. Mouse liver tumors (hepatocellular adenomas and carcinomas) and rat mononuclear cell leukemia (MCL) were reported in both sexes in two lifetime inhalation bioassays employing different rodent strains, and mouse liver tumors were also reported in both sexes in an oral bioassay (NCI, 1977). Tumors

> reported in a single inhalation bioassay include kidney and testicular interstitial cell tumors in male F344 rats (NTP, 1986), brain gliomas in male and female F344 rats (NTP, 1986), and hemangiomas or hemangiosarcomas in male Crj:BDF1 mice (JISA, 1993)."

> "The NTP (1986) study was utilized for modeling the increased incidence in renal cancers, brain cancers, and testicular tumors with treatment reported only in this bioassay."

Further, as indicated in Table 5-18 of the IRIS Toxicological Review, US EPA calculated potency values for a variety of mouse and rat tumors using both NTP (1986) and JISA (1993) data sets. Thus, contrary to the commenter's assertion, it appears that US EPA found the NTP (1986) study to be of sufficient quality to be considered in its quantitative dose-response evaluation.

CalChamber mischaracterizes the NRC (2010) and US EPA positions on the use of NTP (1986) rat kidney tumor data, stating incorrectly that, "Use of the rat kidney tumor data [...] is in stark contrast to the position of every other regulatory body that has had expert peer review and critical toxicology input on the topic [...]"

On the contrary, the NRC peer review report, at page 71, stated:

> "Renal-tubular adenoma and carcinoma were observed in male rats in the NTP (1986) bioassay and to a lesser extent in the Japan Industrial Safety Association (JISA 1993) studies.
>
> "There is a very low spontaneous incidence of renal tumors in Fischer 344 rats (Haseman *et al.* 1998). Induction of renal tumors in rats by tetrachloroethylene is therefore easily observed against a low background. In addition, the controls had only benign tumors, not malignant tumors, whereas the high-dose group had two malignant tumors. In the draft IRIS assessment, EPA calculates the chance that two animals will have a rare tumor to be less than 0.001, giving biological relevance to the finding.
>
> "Overall, the dose-dependent induction of renal tumors in one experiment against the low background incidence of renal tumors in rats exposed to tetrachloroethylene indicates that tetrachloroethylene can induce renal tumors in rats. After integrating the results of the studies, the committee concluded that tetrachloroethylene induces renal tumors in rats. EPA considers the renal tumors to be suggestive of an effect and notes that it is similar to the effects of other chlorinated ethanes and ethylenes. The committee agrees with EPA's assessment."

At page 73 of the NRC report, the expert panel states:

> "The draft IRIS assessment concludes that a mutagenic mode of action cannot be ruled out. The committee agrees with this assessment. A mutagenic mode of action is supported by the findings after exposure to the structurally similar trichloroethylene.

> "While the mode of action of tetrachloroethylene tumorigenesis is not understood, the α2μ-globulin nephropathy and peroxisome proliferator modes of action are not consistent with experimental results. A mutagenic mode of action cannot be ruled out."

Finally, regarding the question of renal α2u-globulin nephropathy, the OEHHA document included a detailed discussion of this issue and why it is unlikely to be relevant in the case of rat kidney tumors induced by PCE exposure.

CalChamber Specific Comments 6, 7, and 8

"Comment 6: On page 22, OEHHA departs from standard toxicology practice, as well as that of U.S. EPA and the recommendation of the NRC (2010) in its peer review of PCE, in combining multiple tumor types. In fact, once rat kidney and leukemia data are properly removed from Table 4, none of the NTP (1986) rat endpoints are statistically significant (see Table 4 footnote 'c') and OEHHA can properly focus on the JISA (1993) data set. If OEHHA declines to adopt the U.S. EPA approach or incorporate these revisions, an independent Peer Review Panel should be asked to address the question, 'Is it scientifically valid and appropriate to include, and combine, all the NTP endpoints to derive the 'multiple tumor' URFs shown in OEHHA"s table on page 22 for use in a human potency factor?' This combination implies all the endpoints are equally relevant to humans, and that all endpoints are equally robust, which is scientifically not the case as detailed in specific comments above.

"Comment 7: On page 22, OEHHA departs from standard toxicology practice and also crosses over studies to derive a 'geometric mean' for a human health cancer potency factor. While this approach is sometimes used for ecological risk assessment, this is uncommon practice in modern toxicology methods for human risk assessment. An appropriately qualified independent peer review panel should thus be charged with the question, 'Is it appropriate for OEHHA to estimate human PCE health risks using a geometric mean for multiple studies and cancer endpoints combined, or should OEHHA select a key, relevant cancer endpoint and estimate cancer risks for that specific (and appropriately sensitive) cancer endpoint?' If the approach is retained, the reason for OEHHA"s departure from selecting a key study (as U.S. EPA guidance and the NRC 2010 peer review report recommended) to prefer a nonstandard method (adopting a geometric mean approach) should be clarified.

"Comment 8: The method OEHHA uses to arrive at the PCE inhalation potency factor on page 22 is inconsistent with the U.S. EPA guidance for human health toxicity value development, and also inconsistent with other state and international (Canada, France, etc.) human toxicology and health risk assessment guidance on the topic. No authoritative health body recommends against selecting a key study in favor of generating a 'geometric mean' across studies in different species. U.S. EPA (2005) Guidelines for Carcinogen Risk Assessment also do not infer concordance across species. We recommend OEHHA follow a validated, authoritative method that includes key study selection and is consistent with other U.S. methods for human health risk assessment."

Response to CalChamber Specific Comments 6, 7, and 8

CalChamber takes issue with OEHHA's use of dose-response data from more than a single key study, as well as using a geometric mean value to derive the proposed cancer potency value. CalChamber appears to believe that there is only one acceptable and accepted way to choose the primary data set for dose-response analysis and only one acceptable and accepted method of choosing the best potency factor from a set of possible candidates. OEHHA disagrees with CalChamber's assertions.

The cancer TSD suggests, as a default option, identifying a single study that represents the best estimate of potency, but does not prohibit using alternative methods (e.g. geometric mean) for deriving potency factors. In the case of PCE, OEHHA judged that both the JISA (1993) and the NTP (1986) studies provided acceptable and non-redundant dose-response information suitable for a quantitative estimate of cancer potency. However, as we noted in several sections of the document, the NTP (1986) study, while important to include in the quantitative determination, was also considered to be more uncertain for reasons stated in the document.

Given that the candidate potency values are each impacted by uncertainty, and given that OEHHA considered some of the higher potency estimates to be more uncertain, the Office decided to use the first of the four selection options presented in the California Department of Health Services cancer risk assessment guidelines (CDHS, 1985). OEHHA chose a mid-range potency from the available values (i.e., the geometric mean) as a "best estimate" for PCE's cancer potency, a value that the Office also judged to be "adequate to protect public health."

Calculating the geometric mean of the potencies is equivalent to determining the median of a log-normal distribution defined by these values. US EPA has used this method occasionally (e.g., see the current US EPA IRIS slope factor for DDT) (US EPA,

2016). An example in which OEHHA has used a geometric mean value is the Public Health Goal for methyl-t-butyl ether (MTBE) (OEHHA, 1999).

Finally, we also provide the following discussion on this topic from a recent textbook on health risk assessment (Theodore and Dupont, 2012, at page 216):

> "In deriving slope factors, the available information about a chemical is evaluated and an appropriate data set is selected. [...] If animal data are used, the species that responds most similarly to humans (with respect to factors such as metabolism, physiology, and pharmacokinetics) is preferred. When no clear choice is possible, the most sensitive species is given the greatest emphasis. <u>Occasionally, in situations where no single study is judged most appropriate, yet several studies collectively support the estimate, the geometric mean of estimates from all studies may be adopted as the slope factor. This practice ensures the inclusion of all relevant data</u>." (emphasis added)

CalChamber Specific Comment 9

"Despite contentious scientific issues related to the Chiu and Ginsberg (2011) model for PCE metabolism, OEHHA considers the Chiu and Ginsberg model to be the best available methodology for estimating dose metrics in the dose-response assessment. This is a departure from U.S. EPA (2012) recommendations on what Chiu and Ginsberg (2011) modeling can (and cannot) confirm, based on the variability of up to 3,000 in relation to one pathway that occurs in humans. For a model (revised by OEHHA in Appendix A) to be used in the PCE update, it should be validated and independently verified by third party (peer review) PBPK modeler(s) prior to acceptance. Then, it should be confirmed to be 'fit for purpose' as the U.S. EPA had done with its interpretation of the 2011 model. Neither the general public nor California lawmakers should be expected to understand Appendix A and its implications on the OEHHA PCE cancer potency value. The independent peer review panel should be asked whether this model is appropriately used and should be able to confirm or refine its use in the PCE potency value."

Response to CalChamber Specific Comment 9

OEHHA refers the commenter to the responses to DoD Specific Comments 1 and 15 which address the issues raised by this comment.

CalChamber Specific Comment 10

"California citizens will be told their PCE cancer risk is 23 times higher than U.S. EPA would calculate (at the same PCE air concentration) for citizens of Arizona or Nevada,

complicating human health risk assessment of shared PCE impacts from point sources whose emissions might cross state boundaries. The California public will not have an 'apples to apples' comparison of their own health improvements over time as compared to the health of other basins or states. This implication, particularly on neighboring states within U.S. EPA Region 9, highlights a significant disconnect between OEHHA and the remainder of the U.S., warranting complete and transparent independent peer review."

Response to CalChamber Specific Comment 10

The CalChamber comment refers to potential regulatory complexities that are beyond the scope of the document analysis and OEHHA's responsibility, which in this case, is to develop a cancer potency value for PCE based on up-to-date scientific information and our cancer TSD (OEHHA 2009). CalChamber's implication that OEHHA should consider PCE impacts in neighboring states as a factor in conducting its own PCE risk assessment would actually undermine OEHHA's statutory responsibility to conduct its risk assessments based purely on scientific criteria. And, as previously stated, the upcoming SRP review constitutes the statutorily mandated peer review of the draft PCE assessment.

CalChamber Specific Comment 11

"In Appendix B on page 42, contrasting details of the JISA (1993) and NTP (1986) studies emphasizes another area where OEHHA departs from best practices: In modern standard toxicology, scientists preferentially rely quantitatively upon studies that are as close to the anticipated inhalation concentration in the 'real world' exposure as possible. This [is] among the many reasons why U.S. EPA and its NRC (2010) peer reviewers downgraded the NTP (1986) study in favor of the JISA (1993) study when selecting the key PCE inhalation cancer study. While neither PCE inhalation cancer study included exposures truly reflective of current California air concentrations, the JISA dose levels are far closer than those used in the NTP study. Specifically, the 1993 JISA data was for PCE exposures at three dose levels (10 ppm, 50 ppm, and 250 ppm for mice). While even the lowest JISA dose level of 10,000 ppb (10 ppm) PCE is still 333,333-times higher than the 2013 PCE air concentration of 0.03 ppb measured in some California air (SCAQMD 2015), it is inconsistent with current scientific practice for OEHHA to use the far higher NTP (1986) concentrations with the more appropriate JISA data available.

"California's health will be protected by use of the more relevant JISA (1993) inhalation study data which are closer to the actual/anticipated PCE exposures that could be encountered in 2016 and beyond. U.S. EPA and its peer review panel did not use the

NTP (1986) study because it failed to have a sufficient number of doses (e.g., two in the NTP study, versus three used in the JISA dataset) to have an acceptable dose-response curve. In addition, the JISA requires less extrapolation to relevant concentrations among the purview of regulatory agencies (i.e., the lowest JISA dose was far closer to the air concentrations being assessed than the NTP 1986 dose ranges). If the NTP (1986) data is retained for quantitative use in the PCE potency factor update, OEHHA should transparently explain the rationale for citing a lesser quality, two- dose, high-dose study over the more recent, better quality, three-dose, lower-dose data set. Further, OEHHA should explain why it is has elected to disregard the U.S. EPA (2005) Guidelines for Carcinogen Risk Assessment regarding preference for low-dose studies designed to avoid excessive extrapolation for use in human health risk assessment. The Peer Review Panel charge questions should include, 'Is the dose range in the key study/studies that form a quantitative basis for the OEHHA potency factor update relevant to current and future California exposures being assessed?' "

Response to CalChamber Specific Comment 11

OEHHA disagrees with the commenter that its use of both the JISA (1993) and the NTP (1986) rodent study data "departs from best practices." The document noted, in this case agreeing with US EPA, that the JISA (1993) study had an advantage of testing animals at several lower doses than the NTP (1986) study. However, OEHHA deemed it important to also use the NTP (1986) data. We also note that US EPA (2012) used the NTP (1986) study data in developing a list of candidate dose-response values, and considered these values in its final deliberations. OEHHA also refers CalChamber to our response to DoD Specific Comment 3, that provides further support for use of both the JISA (1993) and NTP (1986) data.

Regarding US EPA (2005) guidelines and a preference for using lower-dose studies, we agree with US EPA on this issue, but point out to CalChamber that the preference is conditional on other aspects of the studies being equal. In the present case, aside from differing dose levels the studies are not equivalent in terms of animal models tested, as described above.

CalChamber Specific Comment 12

"According to the U.S. EPA Risk Characterization Handbook (2000) guidelines on transparency, as well as the NRC (2010) reminder on best practices, it is expected that any human health risk assessment will clearly and transparently convey to the public the certainty with which a cancer potency value is developed, and avoid inference of a 'false sense of certainty.' In contrast to this expectation, the OEHHA PCE potency value

Public Review Draft contains no uncertainty analysis, which may lead to the presumption the toxicity value put forth is a scientific fact, as opposed to a calculated value that departs from mainstream validated procedures used elsewhere in the U.S. and the world. The Draft should be revised to include an uncertainty analysis with clear and transparent discussion of the uncertainty related to the cancer potency value including all deviations from generally recognized good practice and potential implications of the approach taken."

Response to CalChamber Specific Comment 12

We disagree with CalChamber that the document "contains no uncertainty analysis." In developing the cancer potency factor for PCE, OEHHA discussed various aspects of uncertainty throughout the document. OEHHA refers the commenter to its response to DoD's General Comment for further discussion of this issue. Based on the comment, however, we have provided additional discussion in the document on several of the more important aspects of uncertainty.

CalChamber Specific Comment 13

"The reports and/or guidance detailed below (or their underlying technical methods) are likely to be impacted by the OEHHA draft PCE potency value change. It is unclear whether the wide-ranging impacts across multiple California programs were appropriately considered, as these efforts are not cited in the OEHHA draft PCE development. Because impacts of the OEHHA draft on these and other California initiatives could be substantial, a regulatory impact analysis (including consideration of the financial burden of updating all methodologies that involve PCE health risk assessment in the state of California, relative to the benefit of increasing the PCE cancer potency value) should be conducted:

- South Coast Air Quality Management District (SCAQMD). 2015. Multiple Air Toxics Exposure Study in the South Coast Air Basin (MATES). May. http://www.aqmd.gov/docs/default-source/air-quality/air-toxic- studies/mates-iv/mates-iv-final-draft-report-4-1-15.pdf?sfvrsn=7.
- California Regional Water Quality Control Board (RWQCB). 2007. http://www.waterboards.ca.gov/rwqcb2/water_issues/available_documents/esl.pdf"

Response to CalChamber Specific Comment 13

The Office develops potency values for carcinogenic substances that are candidate Toxic Air Contaminants (TACs) (Health and Safety Code Section 39660) or are listed

under the Air Toxics Hot Spots Act (Health and Safety Code Section 44321). These values are used in the Air Resources Board's (ARB's) air toxics control programs and also by other State regulatory bodies, to estimate cancer risk in humans.

OEHHA is not statutorily mandated to carry out the analyses requested by the commenter.

CalChamber Specific Comment 14

"The assessments and guidelines detailed below do not appear to have been adequately considered, cited or incorporated sufficiently in the OEHHA draft PCE development document:

- While NRC (2010) is cited in the OEHHA assessment, OEHHA did not implement the NRC (2010) findings (as detailed in specific comments above). The Peer Review Panel should require that deviations from the NRC (2010) recommendations are identified clearly and discussed transparently to assist the public in understanding why OEHHA concludes it must differ from the NRC.
- In 2007, the Environmental Council of States advocated for 'assessments which have been externally and independently peer reviewed, where reviewers and affiliations are identified. Other things being equal, there should also be a preference for assessments with more extensive peer review. Panel peer reviews are considered preferable to letter peer reviews.' As noted in General Comment 4, such a review would improve the quality of OEHHA"s PCE draft and provide a medium for OEHHA to justify decisions on deviating from findings in the U.S. EPA IRIS assessment of PCE and its many transparent peer reviews including NRC (2010) and public comment. When set side-by-side with the U.S. EPA IRIS assessment of PCE and its many transparent peer reviews including NRC (2010) and public comment, it is obvious that the less extensive 'peer review in 2016 by the State’s Scientific Review Panel on Toxic Air Contaminants' does not fully meet externally and independent peer review criteria.
- As a final point, we encourage OEHHA to consider U.S. EPA's Science and Technology Policy Council's Peer Review Handbook, 4th edition, October 2015 as a resource for guidance on best practice in peer review. If OEHHA elects not to follow recommendations on peer review set forth in the U.S. EPA 2015 Handbook, the rationale for not undertaking an independent external peer review of the PCE draft potency value should be clearly stated in the document.

"The approaches outlined above have been relied upon nationwide by the U.S. Environmental Protection Agency and other states, and, indeed, in other nations.

OEHHA is encouraged to apply these same balanced and scientifically sound approaches."

Response to CalChamber Specific Comment 14

OEHHA has independent responsibility under California law to develop cancer potency values for protecting the health of people living in California. In updating PCE's cancer potency factors, OEHHA relied primarily on our cancer TSD and other previously developed OEHHA guidance, where relevant.

In developing the cancer TSD, OEHHA scientists critically assessed US EPA's cancer risk assessment methods as documented in their 2005 guidelines (US EPA, 2005). OEHHA agrees with various aspects of US EPA's methods, and thus portions of the cancer TSD are consistent with US EPA guidance. However, OEHHA's methodology is not the same as US EPA's (and where it differs, it tends to be more health-protective). The commenter may refer to the cancer TSD for additional details.

Before finalization, draft cancer potency documents developed by OEHHA are independently reviewed by the Scientific Review Panel on Toxic Air Contaminants (SRP), established by the California Health and Safety Code, Section 39670. We refer CalChamber to this California law for more information on the scientific qualifications of the SRP members. OEHHA may, on a case-by-case basis, utilize information developed by the NRC working groups, but is not bound by federal peer-review processes.

OEHHA has used the best available risk assessment methodology and toxicity data in estimating PCE's cancer potency factors for California. The potency value provides an adequate level of safety in consideration of the numerous irreducible uncertainties in the available toxicity data. It should be noted that federal air pollution law does not preclude California from independently defining health criteria that are more protective (i.e., more restrictive) than those defined by US EPA.

4. Responses to Comments Received from the Halogenated Solvents Industry Alliance (HSIA)

HSIA Comment 1

"MCL lacks relevance for humans."

"In its review of the draft IRIS assessment in 2010, the majority of the NRC panel recommended against the use of MCL data from F344 rats to calculate a cancer slope factor for regulatory use."

"HSIA urges OEHHA to reconsider recommending a cancer potency value based on the MCL data. Its propensity to develop spontaneous MCL shows that the F344 strain does not reflect either the general human population or any significant sensitive sub-population."

"As noted in the NRC review of the draft IRIS assessment, 'NTP has decided to stop using its F344/N rat colony in its bioassays for reasons that include the high background rate of MCL'..."

"The NRC panel judged that "the use of the MCL data could be justified only if it is EPA's policy to choose the most conservative unit risk when considering options but that such justification should be distinguished as a policy decision, not a scientific one."

" [T]he weight of the evidence does not justify use of the F344 rat MCL data for risk assessment."

Response to HSIA Comment 1

The document provides a detailed discussion to support OEHHA's use of rat MCL in the dose-response assessment, to which we refer the commenter. OEHHA also refers the commenter to our responses to DoD Specific Comments 4 and 5, which provide further support for the use of rat MCL in our analysis.

In addition, regarding the NRC panel statement noted in the comment, that using rat MCL represents a "policy decision, not a scientific one," OEHHA strives to determine potency estimates that are "appropriate to protect human health," a policy stated in our cancer TSD. In so doing, we believe it scientifically prudent to consider and make allowances for data gaps and uncertainties in the available toxicologic information. We also note that the potency value obtained from the rat MCL data is not the highest ("most conservative") estimate that could be obtained. In OEHHA's analysis, the highest estimate was obtained by calculating the combined risk of four tumor types found in the NTP rat study.

HSIA Comment 2

"OEHHA inappropriately minimizes the uncertainty associated with the glutathione conjugation pathway in metabolism of PCE."

"...EPA developed a 'harmonized' PBPK model that included consideration of the GSH pathway, but conceded that 'the GSH conjugation pathway in humans remains highly uncertain and/or variable, and that additional data are needed to better quantify that pathway in humans.' "

"An important consideration in evaluating the role of the GSH pathway in PCE toxicity is the exposure dose. Mice have been shown to metabolize PCE to trichloroacetic acid (TCA) to a greater extent than rats; human activity is reported to be even lower than that in rats. In both rats and humans, saturation of this CYP-dependent oxidation of PCE is reported to occur at exposure concentrations of 100 ppm or greater, raising the potential of exposure-dependent metabolite patterns. It should be noted that the F344 rats were exposed to PCE concentrations of 200 and 400 ppm in the NTP (1986) bioassay and 50, 200, or 600 ppm in the JISA (1993) study. In addition to potential impacts on metabolite patterns at/around CYP saturation, consideration must be given to the relevance of bioassay exposure levels to most human exposures.

"As with oxidative metabolism, the primary pathway for metabolism of PCE, *in vitro* studies of GSH conjugation in mice, rats, and humans have shown considerable intra- and interspecies variability. Reported conjugation rates also differ by several orders of magnitude between laboratories. However, in order for GSH conjugation to be relevant in humans, there must be a significant capacity to form glutathione conjugates. In our view, this has not been demonstrated."

Response to HSIA Comment 2

In this comment, HSIA quotes US EPA (2012) that, "the GSH conjugation pathway in humans remains highly uncertain and/or variable..." OEHHA agrees with US EPA (2012) that the PBPK modeling analysis for the GSH conjugation pathway in humans contains a relatively large amount of uncertainty and/or variability, and that additional data are needed to better quantify that pathway in humans. The Office points out, however, that the GSH conjugation pathway could be strongly determined by variability (i.e., actual biological variation within the population) as opposed to uncertainty. Moreover, there is still a large amount of uncertainty regarding the importance of the CYP 450 and/or FMO-3 oxidation branch of the GSH conjugation pathway, which produces additional genotoxic metabolites, and may be more important in humans than in rodents (e.g., see Irving and Elfarra, 2012). Population variability and toxicokinetic uncertainty should properly be addressed by making appropriate health-protective assumptions in the quantitative cancer potency assessment.

The main problem from a regulatory perspective is that the harmonized PBPK model of Chiu and Ginsberg (2011) was not able to decipher how much of the large spread in the model predictions for the GSH conjugation pathway was due to variability and how much was due to uncertainty. In using total metabolism as the preferred dose metric, OEHHA considered the uncertainty in the available scientific information and, in contrast to US EPA, has chosen a modeling approach that will produce a more health-protective potency estimate. This is consistent with the cancer TSD, where OEHHA states its policy of developing cancer potency factors that are "adequate to protect public health."

Based on this comment, however, OEHHA has included additional discussion on the uncertainty/variation in the human PBPK model. Our analysis indicates that this uncertainty has much less impact upon the overall dose-response calculation when using total metabolized dose as the dose metric than might be assumed based on the 3000-fold spread in the PBPK model estimates for human glutathione conjugation. OEHHA finds that the level of "conservatism" added to the analysis by including the GST-pathway in the total dose-metric, is a factor of 10, approximately.

Related to this, HSIA also comments that:

> "The notion of a high proportion of PCE being metabolized via the glutathione conjugation pathway is based largely upon the trichloroethylene (TCE) work of Lash and co-workers utilizing a questionable analytical technique. The technique is based on an indirect method developed by Reed and involves liquid chromatographic (LC) separation followed by derivatization and UV detection."

OEHHA points out that the analysis method used by Lash and coworkers has been a standard and widely used method in glutathione metabolism research and that Lash *et al.* (1999), for example, looked into whether their TCE results could be in error and have repeatedly confirmed the accuracy of their results. In the above-cited article, they write:

> "Rates of GSH conjugation of [TCE] in human liver and kidney subcellular fractions reported in the present study are up to an order of magnitude greater than those reported by Green *et al.* (1997) [...] The controversy between our present and previous results and those of Green *et al.* (1997) has not been resolved. Differences in analytical methods (radiolabeled substrate with HPLC separation versus derivatization and HPLC separation) may contribute to the discrepancies in measured rates. Beyond this, no other explanations have been found to explain the discrepancies. Corrections were made in the present studies for nonenzymatic DCVG formation and our analytical method involved measurement of the N-dinitrophenyl derivative of DCVG and quantitation with respect to authentic standard. Hence, we were certain of the identity of the measured compound."

Regarding "potential impacts on metabolite patterns at/around CYP saturation," data from PCE metabolism studies and the Chiu and Ginsberg (2011) PBPK model indicate that saturation of the oxidative pathway tends to increase the rate of glutathione conjugation (e.g., by less than a factor of 2 in mice), possibly due to reduced competition for substrate between the two enzymatic pathways. However, this does not indicate that the GSH pathway would not be operative at lower environmental exposures.

HSIA Comment 3

"OEHHA's choice of total PCE metabolism as the dose metric in PBPK modeling is inappropriate."

"HSIA agrees with EPA that the currently available data on the role of GSH conjugation in PCE toxicity do not support using total metabolism as the dose metric for dose-response analysis. We urge OEHHA to reconsider its selection. In addition, given the lack of any defined mechanism linking PCE and MCL in F344 rats, there is no justification for OEHHA's decision to select total PCE metabolism as the dose metric for development of a potency factor based on that endpoint."

Response to HSIA Comment 3

The comment appears to be largely a restatement of HSIA Comments 1 and 2. Therefore OEHHA refers the commenter to our responses to Comments 1 and 2. In addition, in Comment 3, HSIA submits that:

> "[T]here are no data to support a role for metabolites of PCE in the generation of MCL in Fisher F344 rats and that, as affirmed by EPA and the NRC, a role for GSH-derived metabolites in renal or hepatocellular tumors is still controversial and associated with a high degree of uncertainty and variability."

The document provides a detailed discussion of research indicating that the metabolism of PCE in rodents produces a variety of reactive and potentially genotoxic (and therefore potentially tumorigenic) metabolites through both the CYP450 oxidation and GST conjugation pathways. Several of these metabolites are stable enough to circulate widely throughout the organism and thus impact tissues other than the liver or kidney. In addition, the document notes that tissues other than the liver or kidney can also independently metabolize PCE to potentially genotoxic metabolites (e.g., the document points out that lymphocytes have been found to contain a variety of CYP isoforms that could oxidize PCE or one of its metabolites).

However, the document also notes that the precise mechanisms by which these potentially genotoxic substances cause increased tumor formation are unknown. Nonetheless, OEHHA's cancer TSD does not require complete knowledge of a chemical's mode of action, nor does it require evidence of tumor concordance between the animal model and humans in order to use the dose-response data for estimation of the cancer potency.

Regarding the involvement of GSH-derived metabolites in rat liver tumors, the document discusses the multiple branch points that occur in the GST conjugation pathway, one of which involves CYP450 or Flavin monoxygenase-3 (FMO-3) oxidation of TCVC to potentially genotoxic α,β-unsaturated sulfoxides. This pathway could occur substantially in the liver, given its relative abundance of CYP450 and FMO-3 enzymes. Regarding rat kidney tumors, the NRC (2010) peer review report, at page 73, states (references omitted):

> "The draft IRIS assessment concludes that a mutagenic mode of action cannot be ruled out. The committee agrees with this assessment. A mutagenic mode of action is supported by the findings after exposure to the structurally similar trichloroethylene. Some metabolites derived from S-(1,2,2-trichlorovinyl) glutathione (TCVG), the glutathione conjugate of tetrachloroethylene, have been shown to be mutagenic in bacterial systems or to cause unscheduled DNA synthesis. Others react with DNA in vitro. S-(1,2,2-Trichlorovinyl)-L-cysteine (TCVC) causes a greater response than dichlorovinyl cysteine in mutagenicity tests using Salmonella and in renal toxicity."

5. References Cited by OEHHA in its Responses

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