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March 30, 2016

Dr. John Budroe
Chief, Air Toxicology and Risk Assessment Section
Air, Community, and Environmental Research Branch
Office of Environmental Health Hazard Assessment
1515 Clay Street, 16th Floor
Oakland, CA, 94612

Via Electronic Mail to John.Budroe@oehha.ca.gov

RE: OEHHA PUBLIC REVIEW DRAFT PERCHLOROETHYLENE (PCE) INHALATION CANCER UNIT RISK FACTOR (POTENCY VALUE) RELEASED FEBRUARY 16, 2016 (45-DAY PUBLIC REVIEW PERIOD ENDS APRIL 1, 2016)

Dear Dr. Budroe:

The California Chamber of Commerce thanks you for the opportunity to submit comments to the Office of Environmental Health Hazard Assessment (OEHHA) regarding its Draft Perchloroethylene (PCE) Inhalation Cancer Unit Risk Factor (Potency Value). This letter provides general comments on areas for increased transparency and scientific rigor in the referenced PCE inhalation potency factor update. At the conclusion of our letter, we have also attached a more detailed set of comments for specific sections of the draft review document.

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 $\mu g/m^3$, 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 recourses.

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.

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?"

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.

We thank you for the opportunity to comment and look forward to a revised PCE toxicity value that appropriately incorporates the modern scientific opinions expressed in the IRIS update for PCE. Should you have any questions on these comments, please feel free to contact me at 916-930-1222.

Sincerely,

Anthony Samson
Policy Advocate

AS:mm

ATTACHMENT

Specific Comments on Public Review of Draft OEHHA PCE Inhalation Cancer Unit Risk Factor

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.

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 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.

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.

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.

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?"

Specific 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.

Specific 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.

Specific 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.

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.

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.

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 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?"

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.

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

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.