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IN REPLY REFER TO:

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Ser N40/348  
March 31, 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

Dear Dr. Budroe,

**SUBJECT: DRAFT INHALATION CANCER UNIT RISK FACTOR FOR  
PERCHLOROETHYLENE**

On behalf of the military services in California, thank you for the opportunity to comment on the Office of Environmental Health Hazard Assessment (OEHHA) Draft Inhalation Cancer Unit Risk Factor (URF) for Perchloroethylene (tetrachlorethylene). Toxicity factors are necessary to assess human health risks during the baseline human health risk assessment and to conduct risk-based cleanup in the Defense Environmental Restoration Program.

These comments are based on our review of the Air Toxics Hot Spots Program, Perchloroethylene Inhalation Cancer Unit Risk Factor, Technical Support Document for Cancer Potency Factors, Appendix B, Public Review Draft, February 2016; provided by the Air, Community and Environmental Research Branch via:  
[http://www.oehha.ca.gov/air/hot\\_spots/021216pcepublicreview.html](http://www.oehha.ca.gov/air/hot_spots/021216pcepublicreview.html).

Several Environmental Protection Agency (EPA) policy and guidance documents have firmly established a hierarchy of preferred toxicity factors for identifying, evaluating, selecting, documenting and communicating toxicity values for use in site-specific human health risk assessments; primarily the following:

- a. EPA's Office of Superfund Remediation and Technology Innovation issued guidance as Directive 9285.7-53,
- b. Office of Solid Waste and Emergency Response (OSWER) Directive 9285.7-53 (2003 Toxicity Value Hierarchy),
- c. OSWER Tier 3 Toxicity Value White Paper 9285.7-86,
- d. Environment Council of the States (ECOS)-Department of Defense (DoD) Sustainability Work Group - Emerging Contaminants Task Group Risk Assessment Provisional Values Subgroup Issue

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Paper "Identification and Selection of Toxicity Values/ Criteria for Comprehensive Environmental Response, Compensation and Liability Act 1980 (CERCLA) and Hazardous Waste Site Risk Assessments in the Absence of IRIS Values, April 23, 2007.

Most importantly, DoD Components are required by the DoDI 4715.18, June 11, 2016 to use the three tier hierarchy of toxicity values prescribed by EPA Guidance and the ECOS. The inhalation cancer potency value derived and published by OEHHA in 1992 is a Tier 3 toxicity value, as it has not been evaluated and published by the EPA IRIS. Further, the current 1992 value is not considered a Tier 2 – Provisional Peer Reviewed Toxicity Value.

We understand that the revised perchloroethylene inhalation URF and Cancer Slope Factor (CSF) for perchloroethylene was revised using the most recent "Air Toxics Hot Spots Program Technical Support Document for Cancer Potency Factors" and is based upon research made available since your last PCE review in 1992. And while OEHHA will be conducting a peer-review of its evaluation, the revised URF/CSF will also be considered a Tier 3 toxicity value in the OSWER hierarchy.

Both the current and the revised URF and CSF are approximately 23 times more stringent than the current IRIS/Tier 1 value as published by the EPA Toxicological Review of Tetrachloroethylene (Perchloroethylene), EPA/645/R-08/011F, February 2012 (EPA 2012). The EPA 2012 review conducted an extensive analysis of the available data regarding PCE health effects and carcinogenicity, and underwent extensive public and expert peer review by the National Research Council. Specific comments regarding the toxicological analysis and to improve the clarity and transparency of the Public Review Draft are attached.

On behalf of the military services in California, please consider this input to ensure a consistent use of scientifically based toxicological factors at National Priority List (NPL) sites in order to provide effective protection of human health and the environment in California.

My point of contact for this is David Bell who can be reached at (415) 977-8845 or Michael Huber at (619) 532-2303.

Sincerely,



C. L. STATHOS  
Deputy Regional Environmental  
Coordinator

1. **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.
2. **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.
3. **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.
4. **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) study instead of the results from the JISA (1993) study requires a clear and transparent explanation in the text.

5. 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.
6. Specific Comment 5, Page 15, Section 7, Paragraph 1. 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.
7. 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.

8. 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, 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.
9. 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.
10. Specific Comment 9, Page 21, Section 9, Bullet list. For Bullet 1, it is not clear why the tissue-specific URF for 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.
11. 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.

12. 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  $(\text{body weight})^{2/3}$  rather than  $(\text{body weight})^{3/4}$  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  $(\text{body weight})^{3/4}$  is used.

It is not clear if OEHHA is following its 2009 guidelines, current EPA standard practice, some combination of the two, or some other set of decision criteria and procedures. Since the set of procedures are not clearly defined, some of the following comments that question the basis for the procedures used may or may not be relevant. It would be most useful if OEHHA were to update its 2009 guidelines to reflect its current practice, if this document is a reflection of the current practice.

13. 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.

14. 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  $\beta$ -lyase cleavage of TCVC since  $\beta$ -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 (n 5 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 ( $V_{max}/K_m$ ) 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.
15. 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.
16. 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.
17. 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.
18. 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  $\alpha$ 2u-globulin nephropathy in the male rat, and PPAR $\alpha$  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.

19. Specific Comment 18, Dose-Response Assessment, Page 20, 1<sup>st</sup> 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 ( $q_1^*$ )." 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  $q_1^*$  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  $q_1^*$  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  $q_1^*$  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  $q_1^*$  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.**

20. 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.

21. Specific Comment 20, Page 22, Table 5. Table 5 is not labeled.

References:

Japan Industrial Safety Association (JISA). 1993. Carcinogenicity Study of Tetrachloroethylene by Inhalation in Rats and Mice. Hadano, Japan.

Liao, A., et al. 2011. Therapeutic Efficacy of FTY720 in a Rat Model of NK-cell Leukemia. *Blood*. 118(10):2793-2800.

National Research Council (NRC). 2010. Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene. Committee to Review EPA's Toxicological Assessment of Tetrachloroethylene, National Research Council. 186 pages.

National Toxicology Program (NTP). 1986. Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS no. 127-18-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP TR 311. Research Triangle Park, NC. U.S. Department of Health and Human Services, National Toxicology Program.

Thomas, KW., et al. 2007. A Review of Large Granular Lymphocytic Leukemia in Fischer 344 Rats as an Initial Step Toward Evaluating the Implication of the Endpoint to Human Cancer Risk Assessment [Review]. *Toxicol Sci*. 99:3-19.

U.S. Environmental Protection Agency (EPA). 2012. Toxicological Review of Tetrachloroethylene (Perchloroethylene). EPA/645/R-08/011F. February.