Responses to Public Comment on the Draft Reference Exposure Levels for Toluene

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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On December 1, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) released the draft document, *Toluene Reference Exposure Levels: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* to solicit public comment. Responses to comments received on the draft toluene reference exposure levels (RELs) are provided here.

Background

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360(b)(2)). OEHHA developed a Technical Support Document (TSD) in response to this statutory requirement that describes acute, 8 hour and chronic RELs and was adopted in December 2008. The TSD presents methodology for deriving RELs. In particular, the methodology explicitly considers possible differential effects on the health of infants, children and other sensitive subpopulations, in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, Chapter 731, Statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*). These guidelines have been used to derive new acute, 8-hour and chronic RELs for toluene.

Comments on the Draft RELs for toluene were received from:

- American Chemistry Council (ACC) Toluene & Xylene Panel

Responses to Comments Received from ACC

ACC Comment 1:

"OEHHA is strongly urged to consider the extensive and scientifically relevant literature on sensory irritation by alkyl benzenes."

"OEHHA has failed to consider a large body of literature on toluene-induced sensory irritation and other alkyl benzenes…."

Response to ACC Comment 1:

OEHHA did consider sensory irritation as a critical endpoint in the derivation of toluene RELs, and included the major studies on toluene-induced sensory irritation as references. In fact, the proposed Acute Reference Exposure Level (REL) for toluene was based on the critical effect of sensory irritation of the eyes and nose.

OEHHA preferred not to base the toluene acute REL derivation on sensory irritation studies using mixtures of alkyl benzenes since there exists an extensive and scientifically relevant literature on sensory irritation induced specifically by toluene itself.

ACC Comment 2:

"OEHHA is strongly encouraged to explain the basis for discounting the previously established acute REL provided in the scientific peer-reviewed literature by its own scientists (Kuwabara et al. 2007; Collins et al. 2004)."

"The scientific basis for re-evaluating previously established RELs for toluene should be provided, especially in light of the fact that the draft document provides no new relevant data. Have new methods (e.g. BMD modeling) or processes (e.g. application or selection of uncertainty factors) been applied in the re-evaluation? The reason(s) for the re-evaluation should be clearly stated and explained in the document."

Response to ACC Comment 2:

OEHHA chose to reevaluate the previously established toluene RELs because: 1) new human data became available for use as the basis of the 8-hr and chronic RELs, and 2) OEHHA is mandated to reevaluate toluene and other chemicals having the potential to disproportionately impact the health of infants and children under the Children's Environmental Health Protection Act (SB 25).

The prior toluene chronic REL was based on animal data (Hillefors-Berglund et al., 1995). The availability of chronic toluene human toxicity data (Zavalic et al., 1998c) indicated that a reevaluation of the toluene chronic REL was appropriate. The chronic toluene REL reevaluation also provided an opportunity to reevaluate the acute data and apply the new REL methodology to the development of the acute REL.

Additionally, OEHHA has used the methodology described in the 2008 noncancer REL Technical Support Document (TSD) (OEHHA, 2008) to derive new acute, 8-hour and chronic RELs for toluene. This methodology explicitly considers possible differential effects on the health of infants, children and other sensitive subpopulations, and recommends the use of techniques of benchmark dose method (BMD) and physiologically based pharmacokinetic (PBPK) modeling wherever possible in order to address quantitatively the adequacy of acute and chronic RELs to protect the health of both children and adults (OEHHA 2008).

Toluene was included in the list of prioritized toxic air contaminants under the Children's Environmental Health Protection Act (OEHHA, 2001, Table 1A) that were chosen for focused literature review. Reevaluation of the toluene RELs solely for the purpose of applying the 2008 infant/child health-protective noncancer REL methodology would have been entirely appropriate.

In the derivation of proposed toluene RELs, BMD modeling was applied for 8-hr and chronic REL derivations, and an applied uncertainty factor component ($UF_{H\text{-}D}$) of 3.9 was from a PBPK modeling study (Nong et al 2006).

OEHHA accepts ACC's suggestion and has added the reasons for the re-evaluation into the text of the draft document. OEHHA also added a portion to the derivation section of the draft toluene RELs document outlining the differences between the old and new RELs.

ACC Comment 3:

"The basis for both the 8-hour and chronic REL was color blindness. There are two key points in regulating based on color blindness: (1) it is a transient/reversible outcome that resolves after exposure is removed and (2) it is the result of years of exposure (i.e. not a single shift) at specific concentrations. That said, it has been established as the most sensitive endpoint, with more adverse endpoints associated with toluene exposure, such as central nervous system (CNS) and reproductive effects, occurring at much higher concentrations. In other words, these outcomes are protected for. As such, applying highly conservative UF based on a reversible outcome is unsupportable."

Response to ACC Comment 3:

Numerous occupational studies and case reports from inhalation exposure to toluene available in the literature suggest that neurologic effects are the most sensitive endpoint following inhalation exposure to toluene. One of the most studied endpoints at lower exposure levels is color vision deficits.

There is evidence that exposure to toluene results in both transient and persistent effects on neurologic endpoints. For example, Baelum et al. (1985) reported that the neurologic responses, including altered color vision, of rotogravure printers (average long-term toluene exposure of 9 to 25 years) exposed to a single 6.5-hour exposure of 100 ppm toluene did not differ from a control group that had not been previously exposed to toluene, suggesting that the acute effects of toluene on color vision were transient rather than being dependent on previous exposure history. In contrast, Zavalic et al. (1998) reported that analysis of color vision scores in toluene-exposed workers on Wednesday did not differ from the scores in the same workers on Monday after at least 48 hours without exposure, suggesting that the effect was persistent. Thus, toluene-induced color blindness should not be considered a reversible effect, and is suitable for the development of a chronic REL.

ACC Comment 4:

“OEHHA should not only consider the scientific merit of alternate REL endpoints and methods outlined in these technical comments, but also incorporate a thoughtful impact analysis for selection of the toluene RELs, particularly in light of the proposed DTSC regulation [R-2016-08] that appears to elevate OEHHA REL values to the level of California Applicable or Relevant and Appropriate Requirements (ARARs) under multiple regulatory programs.”

Response to ACC Comment 4:

OEHHA is not mandated under Health and Safety Code Section 44360(b)(2) to provide an impact analysis of any type when developing RELs. Further, RELs are purely scientific risk assessment values that must be developed through health-risk assessments, and it is inappropriate to conduct an impact analysis as part of a health-risk assessment. Any questions or comments regarding the use of OEHHA REL values by other Cal EPA departments should be directed to those departments.

ACC Comment 5:

"Nature of the Critical Effect: For risk assessment and toxicity factor development, a critical effect is selected as the basis of this factor. For the acute inhalation REL derivation, OEHHA selected sensory irritation of the eyes and nose as the critical effect from the key study (Andersen et al (1983). The irritation reported in the study was confined to the eyes and nose and therefore, is considered a portal-of-entry effect, and, as such, its occurrence is dependent solely on the ambient air concentration and the sensitivity of those exposed. Internal metabolism plays no role.

Odor detection is mediated through the olfactory nerve whereas irritation to eyes and nasal pungency is mediated through the trigeminal nerve (Cometto-Muniz et al. 2004, 2005; Abraham et al. 2007). Chemesthesis or sensory irritation includes nasal pungency coupled with eye irritation, and is a different effect than odor.

The perception of odor level often grows less with exposure. Such was the case among the subjects in Andersen et al. (1983). Importantly, the subjects in Andersen et al. (1983) were able to distinguish odor from sensory irritation. OEHHA explicitly chose sensory irritation as the critical effect.

These subjects reported a weaker perception of both odor and air quality as exposure continued (Figs. 3 and 4 in Andersen et al. 1983). That subjects in Andersen et al. (1983) were able to distinguish odor from sensory irritation is noteworthy. Solvents such as toluene have an odor with a detectable threshold. Chemesthesis or sensory irritation that includes nasal pungency coupled with eye irritation is a different effect and does not accommodate; accommodation is the gradual decrease in odor perception with continued exposure. Odor detection is mediated through the olfactory nerve whereas irritation to eyes and nose or pungency is mediated largely through the trigeminal nerve (Cometto-Muniz et al. 2004, 2005; Abraham et al. 2007). This distinction is an important one.

Toluene-induced sensory irritation of the nose and eyes is a clearly a portal of entry effect. Therefore, toxicokinetics likely plays no role in the induction and occurrence of this effect and a UF based on toxicokinetics is scientifically inappropriate and unjustified."

"The panel suggests additional references to further understand adult/child differences and include the 1) Appendix C of the Texas Commission on Environmental Quality (TCEQ) issued guidance on developing toxicity factors (TCEQ, 2015). Appendix C of this guidance is a white paper on child-adult differences in inhalation dosimetry. This

appendix provides a brief but well-referenced discussion on applying CFD to evaluate adult/child differences.

Other relevant references include: Brüning et al., 2014; Cometto-Muniz and Abraham, 2016; Doty et al., 2004 Nielsen and Alarie, 1982; Nielsen et al., 2007; Nielsen and Wolkoff, 2017)."

Response to ACC Comment 5:

OEHHA explicitly chose CNS effects (impaired reaction time and symptoms of headache, dizziness, feeling of intoxication) plus sensory irritation to eyes and nose as the critical effect for the acute toluene inhalation REL derivation, not odor detection.

For the uncertainty factors, OEHHA agrees with ACC that since toluene is a direct-acting chemical whose site of action is the point of first contact, toxicokinetics plays no role in this effect. Thus, OEHHA is applying a default UF_{H-k} of $\sqrt{10}$. An intraspecies uncertainty factor with a toxicodynamic component (UF_{H-d}) of 10 is applied for the use of human studies with normal adult subjects and to address the human variation in response to substances with nervous system effects, including sensitive subpopulations such as children (OEHHA 2008), resulting in an overall UF of 30. OEHHA also added descriptions of the Cometto-Muniz and Abraham (2016) and Nielsen and Wolkoff (2017) studies to the document.

ACC Comment 6:

"Uncertainty Factors for Human Toxicokinetic Variability: The overall UF for intraspecies differences or human variability has a default value of 10. The recent historical trend in the use of these factors in regulation is to permit information on toxicokinetics (TK) and toxicodynamics (TD) to inform the UF values (WHO-IPCS, 2005 Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration Assessment,). The overall UF_h for human variability with a default value of 10 was split into two factors: UF_{h-k} and UF_{h-d}, for kinetics and dynamics respectively. The default values for these UFs are either $\sqrt{10}$ of 3.16 for both; alternatively, factors or 2.5 for UF_{h-d} and 4.0 for UFh-k have been suggested (WHO-IPCS, 2005 Chemical-Specific Adjustment Factors for Interspecies Differences and Human Variability: Guidance Document for Use of Data in Dose/Concentration Assessment; USEPA, 2014, Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation). The overall value of 39 used by OEHHA is almost four times the default."

Response to ACC Comment 6:

In the Technical Support Document (TSD) adopted in December 2008, OEHHA published a revised set of default UF values, among which the $UF_{h\text{-}d}$ default value is $\sqrt{10}$ but can be 10 when necessary, accounting for the potential additional susceptibility of children such as exacerbation of asthma and neurotoxicity, while $UF_{h\text{-}k}$ can be 10 to allow for diversity including infants and children with no human kinetic data (Table 4.4.1, OEHHA 2008).

In the actual derivation of the proposed acute REL for toluene, OEHHA used a default value of $\sqrt{10}$ for $UF_{H\text{-}k}$ and a $UF_{h\text{-}d}$ of 10 to account for the potential additional susceptibility of children toward the neurotoxic effects of toluene, resulting in an overall UF of 30.

ACC Comment 7:

"Measures of Human Variability for Sensory Irritation:

Curiously, one notes that the LOAEL from Andersen et al. (1983) for sensory irritation in the critical study is 100 ppm whereas in this laboratory study, toluene-related chemesthesis was not detectable below 1000 ppm. This observation could reflect the variability in the two methods used for exposure, closed chamber vs. local application, or the inability of subjects to distinguish odor from chemesthesis (Andersen et al. 1983; Cometto-Muniz et al. 2001).

One of the first risk assessment approaches for sensory irritation was developed by Neilsen and Alarie (1982). Sensory irritation of the upper respiratory tract in anesthetized mice results in a pause during exhalation and a decrease in respiratory rate. The POD is a 50% decrease or RD50.

Collins et al. (2004) is a paper written by OEHHA staff. In this paper, an acute REL for toluene of 9.8 ppm or 3.7 mg/m^3 was derived from the 1983 Andersen et al. study. Kuwabara et al. (2007) is another paper written by OEHHA staff. In this paper, the acute REL of 9.8 ppm was compared to those calculated with three measured RD50 values from the mouse bioassay (Table 2 in Kuwabara et al.), suggesting close agreement between these derivations.

The relationship of the RD50 and the REL is given by:

$$REL = 0.00026 \times RD_{50}^{1.4}$$

Uncertainty factors for human variability for trigeminal sensory irritation have been proposed in the literature; Neilsen et al. (2007) suggest that a UFh of 5 is sufficient for the general population and a UFh of 10 would be protective of even highly susceptible individuals. Brüning et al. (2014) indicate an UFh of 3 is sufficient. A look back at the figure on the previous page from Cometto-Muniz and Abraham (2016) indicates that the range of detectability for either eye irritation or nasal pungency is likely no more than half a log unit and also suggests this latter value of 3 is the most appropriate option. Applying this value to the NOAEL of 40 and rounding down gives an acute REL value of 10 ppm, identical to those derived by OEHHA personnel in 2007 from the mouse respiratory bioassay results and their earlier evaluation from the human data.

TCEQ (2008) developed an acute reference value (ReV) for toluene corresponding to a 1-hour exposure. In this derivation, TCEQ also used Andersen et al. 1983 as the key study and identified the same POD, which is the NOAEL of 40 ppm. However, they used an intraspecies UF of 10 to obtain a ReV of 4 ppm, 4-fold higher than that derived by OEHHA."

Response to ACC Comment 7:

The implementation of the Hot Spots TSD for Derivation of RELs (OEHHA 2008) resulted in an updating of REL methodology. Since the REL methodology has changed, the relationship between RD50 and REL values described in Kuwabara et al. (2007) is no longer useful to directly derive a REL using the algorithm provided in Kuwabara et al. Additionally, OEHHA policy has always preferred the use of a benchmark dose approach over the use of an RD50 in deriving RELs.

When an uncertainty factor approach is used due to the lack of data for compound-specific models of toxicokinetics and toxicodynamics, an overall intraspecies uncertainty factor (UF_H) of 30 rather than 10 (toxicokinetic component, UF_{H-k} =10; toxicodynamic component, $UF_{H-d} = \sqrt{10}$) will be used as a default procedure to protect infants' and children's health, for example, in cases where differences in metabolism and excretion are key to the toxicological activity. For direct-acting chemicals whose site of action is the point of first contact, a UF_{H-k} of $\sqrt{10}$ may be sufficient. Where significant concern for toxicodynamic differences larger than three-fold is present, a larger UF may be applied, such that the total UF_H could be larger than 30 (OEHHA 2008). Thus, OEHHA will use a default UF_{H-k} of $\sqrt{10}$, and a UF_{H-d} of 10 for additional susceptibility of children toward the neurotoxic effects, resulting in a total intraspecies uncertainty factor (UF_H) of 30.

ACC Comment 8:

"8-hour & Chronic REL:

OEHHA used bench-mark dose/concentration (BMD/BMC) modeling to derive (data-driven) points of departure (POD) for the 8-hour and chronic REL. We agree with using the BMD/BMC method, which is recommended by the USEPA to determine a POD because it uses all data from a study to construct the dose-response relationship v. the NOAEL/LOAEL approach which is constrained by the use of single exposure concentrations. The BMD/BMC method uses the lower bound of the 95th percent confidence limit (CL) to identify the POD.

However, we disagree with the selection of the BMD05 v. BMD10 as the excess risk. USEPA conducted a study to compare the traditional NOAEL/LOAEL method to BMD/BMC, which showed that BMDL/BMCL10 values best correspond to a NOAEL. Based on their study, USEPA recommends applying the BMDL/BMCL10 values for deriving the BMC or BMD (USEPA, 2000 & 2002). Moreover, based on the USEPA guidance, OEHHA's use of the BMCL05, corresponds to a value that is about 2 times lower than a NOAEL. As such, the BMCL10 is most appropriate to identify the (NOAEL) POD for deriving 8 hour & chronic RELs. Finally, the data showing the range of PODs identified by varying the excess risk, for 1, 2.5, 5 and 10, respectively, should also be presented.

Given the data set used by OEHHA is a based on only two groups, the BMD modeling to construct the dose-response relationship for toluene and color blindness has substantial uncertainty, which is acknowledged by OEHHA (page 54), but not quantitatively adjusted. Moreover, as seen in Table 3 (page 51), the BMD models are essentially the same, with nearly identical p- and AIC-values; OEHHA states that they used these values as the basis for model selection, yet they don't provide information that allows a true distinction in model fit."

Response to ACC Comment 8:

A response range of 1% to 5% approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological studies, and in large laboratory animal studies the detectable response rate is typically in the 5 to 10% range (Gaylor, 1992). In 1995, using animal developmental toxicity data, US EPA concluded that a 1% response rate was likely to be too low to be detected and therefore too uncertain to use as a point of departure, while either 5% (BMC05) or 10% (BMC10) response rates were adequate for the purposes of estimating a benchmark concentration (Barnes et al., 1995). One

reason for this conclusion was the large difference (29-fold) between observed NOAELs and the 1% benchmark using developmental toxicity data.

Subsequently, US EPA (2007) used a 10% response rate for benchmark concentrations when deriving chronic inhalation reference concentrations (RfCs). More recently, RfC determinations for various endpoints by US EPA have used either 5% or 10% as the benchmark response rate, depending on the statistical uncertainty in the data (US EPA, 2002; US EPA, 2004).

OEHHA has used the 5% response rate in several chronic RELs, and showed that the lower 95% confidence bound on the BMC05 typically appears equivalent for risk assessment purposes to a NOAEL in well-designed and conducted animal studies where a quantal measure of toxic response is reported (Lewis and Alexeeff, 1989; Alexeeff et al., 1992; Alexeeff et al., 1993; Barnes et al., 1995; Collins et al., 2004; Collins et al., 2005; Starr et al., 2005; Alexeeff et al., 2006; Brown et al., 2006). Therefore, OEHHA typically uses a 5% response rate as the default for determination of the BMC from quantal data (*i.e.* the effect is either present or it is not) in animals (Fowles et al., 1999). Thus, OEHHA does not believe that including BMC01, BMC0.25, and BMC10 modeling data in the REL document is necessary.

On page 54 of OEHHA's toluene RELs document, the only statement involving "uncertainty" is a comment on the US Environmental Protection Agency's (US EPA's) RfC derivation (US EPA 2005), which states, "USEPA (2005) derived a chronic inhalation Reference Concentration (RfC) of 5 mg/m^3 for toluene based on the arithmetic mean of NOAELs (34 ppm) from four studies that measured either neuropsychological tests results or color vision loss. This introduced uncertainty in deriving the point of departure from multiple studies with varied endpoints and varied levels of response". OEHHA does not agree with ACC's comment that "the BMD modeling to construct the dose-response relationship for toluene and color blindness has **substantial** [bolding added] uncertainty, which is acknowledged by OEHHA (page 54), but not quantitatively adjusted". OEHHA does not believe that substantial uncertainty exists in the BMD modeling presented in the document.

Finally, OEHHA provided all the pertinent modeling information for the benchmark dose analysis of the Zavalic et al. (1998c) data in Table 3 on page 51 of the document. OEHHA chose the probit model to provide the point of departure for the REL derivation because it had the lowest Akaike Information Criterion (AIC) value and the highest p-value for goodness-of-fit, and provided the lowest $BMCL_{05}$ level.

ACC Comment 9:

"8-hour REL (only): From the draft toluene document it is not clear to whom an 8-hour REL would apply/protect and under what exposure scenario an 8-hour time period would be encountered by the general public. Conventionally, a 24-hour time period is considered more appropriate."

Response to ACC Comment 9:

In OEHHA's Air Toxics Hot Spots Program Technical Support Document (TSD) for the Derivation of Noncancer RELs adopted in 2008, the new type of 8-hour REL was developed in order to refine the risk assessment approach for the large number of industrial facilities that operate and emit chemicals for 8 hours per day, 5 to 7 days per week and to utilize the advanced features in air-dispersion modeling. The air-dispersion modeling in the Hot Spots Program has traditionally modeled such emissions as if they were uniformly emitted over 24 hours a day, continuously. Advances in computer capabilities have made it feasible to model more accurately the ground level concentrations of these emission scenarios by using meteorology obtained during the time when the facilities are actually operating (generally daytime). The majority of the highly populated areas in California have significant diurnal-nocturnal meteorological differences that can affect the magnitude of the modeled risk and location of receptors (OEHHA, 2008).

The 8-hour REL also aims to protect the offsite workers and children in schools. The chronic noncancer health impacts on offsite workers (individuals working at other worksites in areas impacted by the facility emissions) have been traditionally assessed with the chronic RELs. Because offsite workers generally work 8 hours and not 24, the eight-hour RELs will ensure a more accurate assessment of the health impacts of their exposures. The eight-hour RELs will also be useful for assessing the health impacts of exposure of children in schools, who usually would not spend more than 8 hours a day in schools. Exposure duration for children and offsite workers will vary, but an eight-hour exposure duration assumption would be reasonable, particularly if children and offsite workers are exposed to facility emissions at their school or place of work and not at their residential locations (OEHHA, 2008).

OEHHA will add the above text into the document.

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