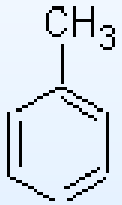
Air Toxics Hot Spots Program

Toluene Reference Exposure Levels

Office of Environmental Health Hazard Assessment

Scientific Review Panel Meeting
June 2019

Toluene



- Widely used as a solvent in paints, coatings, synthetic fragrances, adhesives, inks, and cleaning agents, and is a gasoline constituent.
- Volatile: vapor pressure 28.4 mmHg @25°C
- Readily absorbed via inhalation and ingestion from the respiratory and gastrointestinal tracts, respectively
- Conversion factor: 1 ppm = 3.76 mg/m^3 @ 25°C

Toluene Acute REL

- Based on Andersen *et al.*, 1983 study
- Human study on 16 young and healthy males
- Inhalation exposure of 0, 10, 40 or 100 ppm for 6 hours
- Critical effects: Impaired reaction time and symptoms of headache, dizziness, feeling of intoxication, sensory irritation (eye and nose irritation)

Original Acute REL (2008)

Key Study	**Andersen *et al.*, 1983**
LOAEL	**100 ppm**
NOAEL	**40 ppm**
Exposure duration	**6 hours**
Time-adjusted concentration	**98 ppm (370 mg/m³)**
LOAEL uncertainty factor	**1**
Interspecies uncertainty factor	**1**
Intraspecies uncertainty factor	**10**
Cumulative uncertainty factor	**10**
Acute REL	**37,000 µg/m³ (9,800 ppb)**

Proposed Acute REL

Key Study	**Andersen *et al.*, 1983**
LOAEL	**100 ppm**
NOAEL	**40 ppm**
Exposure duration	**6 hours**
Time-adjusted exposure	**40 ppm (no time adjustment for sensory irritation) (150 mg/m³)**
LOAEL uncertainty factor (UF_L)	**1**
Interspecies uncertainty factor	**1**
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	**√10 (default)**
Toxicodynamic (UF_{H-d})	**10**
Cumulative uncertainty factor	**30**
Acute REL	**5,000 µg/m³ (1,300 ppb)**

Changes from Prior Acute REL

	Prior	Proposed
Time-adjusted concentration	370 mg/m^3	150 mg/m^3
LOAEL uncertainty factor (UF_L)	1	1
Interspecies uncertainty factor	1	1
Intraspecies uncertainty factor	10	30
Toxicokinetic (UF_{H-k})	√10	√10
Toxicodynamic (UF_{H-d})	√10	10
Cumulative uncertainty factor	10	30
Acute REL	37,000 µg/m^3	5,000 µg/m^3

- Due to the concentration-dependent nature of sensory irritation endpoint, no time-adjustment applied for proposed acute REL
- Toxicodynamic component of 10 for greater susceptibility of children to neurotoxic effects

Original Chronic REL (2000)

Study	Hillefors-Berglund *et al*. 1995
Study population	Male Sprague-Dawley rats
Exposure method	Inhalation
Exposure duration	6 hr/d, 5d/wk for 4 wks
Critical effects	Decreased brain weight and altered dopamine receptor binding
LOAEL	80 ppm
NOAEL	40 ppm
Time-adjusted exposure	7 ppm (40 x 6/24hr x 5/7days)
Subchronic uncertainty factor	10
Interspecies uncertainty factor	1 (supported by human study)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Chronic REL	300 µg/m³ (70 ppb)

Proposed 8-Hour & Chronic RELs

- **Based on Zavalic *et al.* (1998)**
- **Workers exposed to toluene based on an occupational inhalation rate of 10 m^3/day, 5 days/week for more than 15 years**
- **Worker evaluations performed using a sensitive color vision testing method (Lanthony D-15 desaturated test)**
- **Critical effect: Acquired color vision impairment (Dyschromatopsia)**

Acquired Dyschromatopsia — A Sensitive Human Endpoint

- **Acquired dyschromatopsia is a color vision impairment**
- **Neural alterations in the peripheral nervous system**
- **Can be detected before functional disability, earlier than other endpoints**
- **>50 studies reveal that color vision impairment from chemical exposure can be detected at low exposure levels using sensitive color vision testing method**
- **Occurs at concentrations lower than those for other human toxicity endpoints (Gobba and Cavalleri, 2003)**

Study Data

Study population	**41 adult workers for NOAEL, 32 adult workers for LOAEL, 83 adult workers for control**
Exposure method	**Inhalation**
Continuity	**10 m^3/day occupational inhalation rate, 8 hours/day, 5 days/week**
Duration	**15.60 ± 4.61 years (NOAEL); 19.86 ± 5.61 years (LOAEL)**
Critical effects	**Acquired color vision impairment (dyschromatopsia)**
LOAEL	**156 ppm**
NOAEL	**35 ppm**

Benchmark Dose Analysis

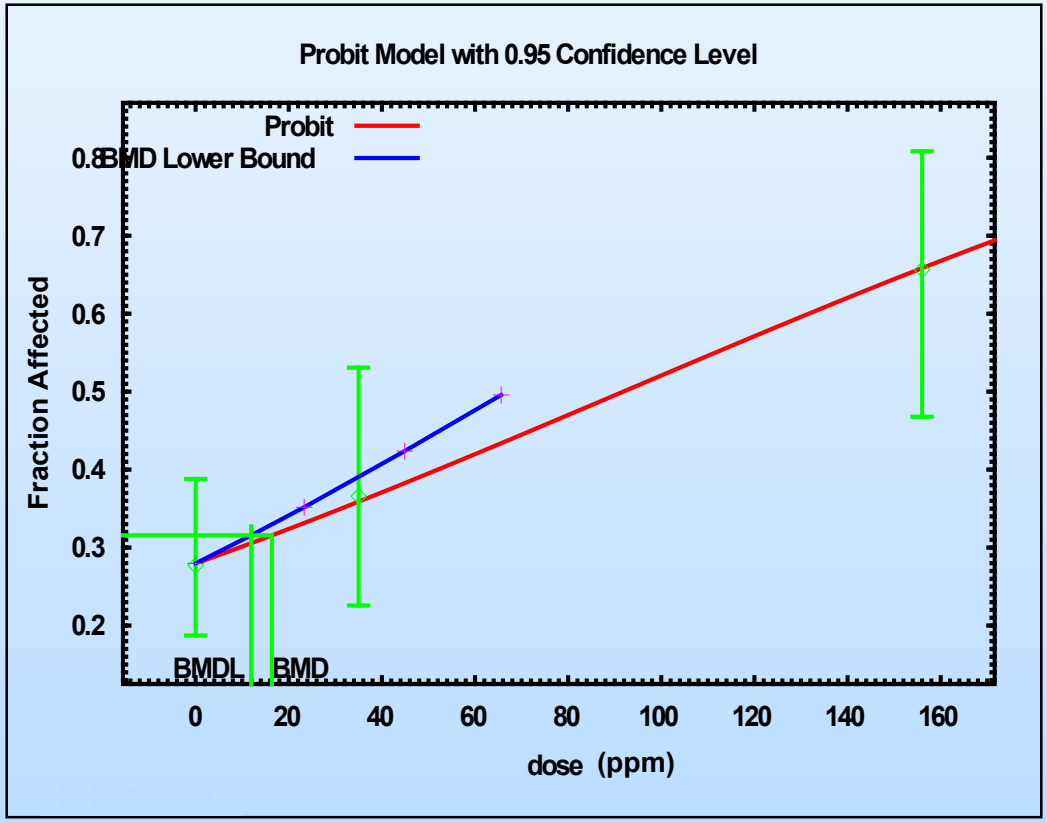
- **Benchmark Dose dichotomous modeling**
- **The BMDL or BMC_{05}, ~NOAEL**
- **The Probit Model provided the best fit**

Model	BMC_{05} ppm (mg/m^3)	$BMCL_{05}$ ppm (mg/m^3)	p-value for fit	AIC*
Probit	16.4 (62)	11.9 (45)	0.9133	197.02
Logistic	16.8 (63)	12.1 (46)	0.8996	197.02
Quantal Linear	11.0 (41)	6.9 (26)	0.8021	197.07
Quantal Quadratic	41.2 (155)	32.0 (121)	0.4726	197.52
Multistage (β=2)	11.0 (41)	6.9 (26)	0.8021	197.07

- **The Probit Model resulted in $BMCL_{05}$ of 11.9 ± 0.12 ppm**

Benchmark Dose Analysis

Probit model fit to Zavalic *et al.* (1998) human dyschromatopsia data



Proposed 8-hour REL

Study	**Zavalic *et al.*, 1998**
LOAEL	**156 ppm**
NOAEL	**35 ppm**
Benchmark dose ($BMCL_{05}$)	**11.9 ppm**
Time-adjusted exposure	**8.6 ppm (11.9 ppm x 8/8hr x 5/7 d/wk)**
LOAEL uncertainty factor (UF_L)	**1**
Subchronic uncertainty factor	**1**
Interspecies uncertainty factor	**1**
Intraspecies uncertainty factor	**39**
Toxicokinetic (UF_{H-k})	**3.9 (Nong *et al.*, 2006)**
Toxicodynamic (UF_{H-d})	**10**
Cumulative uncertainty factor	**39**
8-hour REL	**830 µg/m³ (220 ppb)**

Proposed Chronic REL

Study	**Zavalic *et al.*, 1998**
LOAEL	**156 ppm**
NOAEL	**35 ppm**
Benchmark dose ($BMCL_{05}$)	**11.9 ppm**
Time-adjusted exposure	**4.3ppm(11.9ppm x 10/20m^3 x 5/7d/wk)**
LOAEL uncertainty factor (UF_L)	**1**
Subchronic uncertainty factor	**1**
Interspecies uncertainty factor	**1**
Intraspecies uncertainty factor	**39**
Toxicokinetic (UF_{H-k})	**3.9 (Nong *et al.*, 2006)**
Toxicodynamic (UF_{H-d})	**10**
Cumulative uncertainty factor	**39**
Chronic REL	**420 µg/m^3 (110 ppb)**

Changes from Prior Chronic REL

	Prior	Proposed
Study population	Animal	Human
Critical effects	CNS toxicity	Color vision impairment
Time-adjusted Exposure	NOAEL(30 mg/m^3)	$BMCL_{05}$ (16 mg/m^3)
Subchronic uncertainty factor	10 (< 13 wk)	1 (> 8.4 yr)
Interspecies uncertainty factor	1*	1
Intraspecies uncertainty factor	10	39
Toxicokinetic (UF_{H-k})	√10	3.9 **
Toxicodynamic (UF_{H-d})	√10	10
Cumulative uncertainty factor	100	39
Chronic REL	300 µg/m^3	420 µg/m^3

* Supported by a human study

** Nong *et al.* (2006) PBPK-modeled largest inter-individual toxicokinetic variability of 3.9

Toluene: Toxic Air Contaminant (TAC)

- Toluene was listed as a developmental toxicant in 1991 under Proposition 65
- Based on neonatal effects from maternal toluene abuse during pregnancy
- Neurotoxic effects such as microencephaly, attention deficits, hyperactivity, language development impairment
- Fetotoxic effects of toluene demonstrated in comparable animal studies
- Valid concern that toluene exposure may disproportionally impact infants and children
- OEHHA recommends toluene be identified as a TAC which may disproportionally impact children

Toluene Proposed RELs Summary

Acute:	**3,900 µg/m^3 (1,300 ppb)**
8-Hour:	**830 µg/m^3 (220 ppb)**
Chronic:	**420 µg/m^3 (110 ppb)**

Comments and Responses

During the public comment period, OEHHA received comments from the American Chemistry Council (ACC) Toluene & Xylene Panel. Those comments are addressed below.

Comments and Responses
Sensory irritation by alkyl benzenes

Comment #1: OEHHA has failed to consider a large body of literature on toluene-induced sensory irritation by toluene and other alkyl benzenes.

Response #1: OEHHA based the proposed toluene acute REL on human sensory irritation of the eyes and nose.

Comments and Responses
Basis for re-evaluation

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**
- **The scientific basis for re-evaluating previously established RELs for toluene should be provided**
  - **Have new methods or processes been applied in the re-evaluation?**
  - **The reason(s) for the re-evaluation should be clearly stated and explained in the document.**

Comments and Responses
Basis for re-evaluation

Response #2 :

OEHHA chose to reevaluate the previously established toluene RELs because:

- **OEHHA was 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), and**
- **new human data became available for use as the basis of the 8-hr and chronic RELs.**

Comments and Responses
Basis for re-evaluation

Response #2 continued:

- **In response to comments, OEHHA added the reasons for the RELs re-evaluation and a comparison between the old and new toluene RELs in the text of the draft toluene RELs document.**

Comments and Responses
Color blindness: transient endpoint?

Comment #3: The basis for both the 8-hour and chronic REL was color blindness.

- **Color blindness is a transient/reversible outcome that resolves after exposure is removed**
- **It is the result of years of exposure (i.e. not a single shift) at specific concentrations**

As such, applying highly conservative UF based on a reversible outcome is unsupportable.

Comments and Responses
Color blindness: transient endpoint?

Response #3: There is evidence that exposure to toluene results in persistent effects on neurologic endpoints including color vision deficits.

- **Zavalic et al. (1998) reported that 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.**

Comments and Responses
Impact analysis

Comment #4: OEHHA should incorporate a thoughtful impact analysis for selection of the toluene RELs, particularly in light of the proposed DTSC regulation that appears to elevate OEHHA REL values to the level of California Applicable or Relevant and Appropriate Requirements (ARARs) under multiple regulatory programs.

Response #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. Any questions or comments regarding the use of OEHHA REL values by other Cal EPA departments should be directed to those departments.

Comments and Responses
Nature of the Critical Effect

Comment #5:

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 … Toluene-induced sensory irritation of the nose and eyes is 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.

Comments and Responses
Nature of the Critical Effect

Response #5: OEHHA agreed with ACC that the key effect for toluene acute REL is sensory irritation, and the site of action is the point of first contact; toxicokinetics plays no role in this effect. The document was revised to apply a default $UF_{H\text{-}k}$ of $\sqrt{10}$ and a $UF_{H\text{-}d}$ of 10 for potential sensitive subpopulation (e.g. infants/children) neurotoxicity, resulting in an overall UF of 30.

Uncertainty Factors for Human Toxicokinetic Variability

Comment #6:

The overall UF for intraspecies differences or human variability has a default value of 10. 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 $\sqrt{10}$ or 3.16 for both; alternatively, factors of 2.5 for UF_{H-d} and 4.0 for UF_{H-k} have been suggested. The overall value of 39 used by OEHHA is almost four times the default.

Uncertainty Factors for Human Toxicokinetic Variability

Response #6:

In response to ACC comment #5, OEHHA changed the $UF_{H\text{-}k}$ from 3.9 (based on PBPK data) to a default value of $\sqrt{10}$ for the acute inhalation REL derivation. Use of a $UF_{H\text{-}d}$ of 10 to account for the potential additional susceptibility of children to the toluene-induced neurotoxicity, resulted in an overall UF of 30. This increase in cumulative UF over the default value was entirely appropriate given the toluene neurotoxicity data.

Measures of Human Variability for Sensory Irritation

Comment #7:

Sensory irritation of the upper respiratory tract in mice results in a decrease in respiratory rate. The POD is a 50% decrease or RD50.

Collins et al. (2004) and Kuwabara et al. (2007) are papers written by OEHHA staff, in which the acute toluene REL of 9.8 ppm was compared to RD50 values from the mouse bioassay, suggesting the relationship of the RD50 and the REL by:

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

Measures of Human Variability for Sensory Irritation

Comment #7 continued:

Uncertainty factors for human variability for sensory irritation:

- **Neilsen et al. (2007) suggested UF_H of 5 for the general population and UF_H of 10 for highly susceptible individuals**
- **Brüning et al. (2014) and Cometto-Muniz and Abraham (2016) indicated a UF_H of 3. Applying this value to the NOAEL of 40 ppm and rounding down gives an acute REL value of 10 ppm, identical to those derived by OEHHA in 2007**
- **TCEQ (2008) developed an acute reference value (ReV) for toluene corresponding to a 1-hour exposure using Andersen et al. 1983 as the key study and NOAEL of 40 ppm. Using an intraspecies UF of 10 to obtain a ReV of 4 ppm, 4-fold higher than that derived by OEHHA.**

Measures of Human Variability for Sensory Irritation

Response #7:

Since the acute REL is based on human sensory irritation data, there is no need to consider an animal-based sensory irritation approach for deriving an acute REL. Additionally, OEHHA policy has always preferred the use of a benchmark dose approach over the use of an RD50 in deriving RELs.

The use of a default $UF_{H\text{-}k}$ of $\sqrt{10}$, and a $UF_{H\text{-}d}$ of 10 for potential additional susceptibility of children to neurotoxicity, resulting in a total intraspecies uncertainty factor (UF_H) of 30, is consistent with OEHHA methodology.

Comments and Responses
8-hour & Chronic RELs

Comment #8:

We agree with OEHHA in using the BMD/BMC method for the 8-hour and chronic RELs, which 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 studies showed that BMDL/BMCL10 values best correspond to a NOAEL, and recommends applying the BMDL/BMCL10 values for deriving the BMC or BMD (USEPA, 2000 & 2002). 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.

Comments and Responses
8-hour & Chronic RELs

Comment #8 continued:

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 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.

Comments and Responses
8-hour & Chronic RELs

Response #8:

OEHHA has demonstrated that the lower 95% confidence bound on the BMC05 typically appears equivalent to a NOAEL in well designed and conducted animal studies where a quantal measure of toxic response is reported (Fowles et al., 1999; OEHHA, 2008).

Therefore, OEHHA typically uses a 5% response rate as the default for determination of the BMC from quantal data. Thus, OEHHA does not deem it necessary to include BMC01, BMC2.5, or BMC10 modeling data in the Document.

Comments and Responses
8-hour & Chronic RELs

Response #8 continued:

On page 54 of the public comment toluene RELs document, the only statement involving "uncertainty" is a comment on USEPA's RfC derivation (USEPA 2005). 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 uncertainty, which is acknowledged by OEHHA". OEHHA does not believe that substantial uncertainty exists in the BMD modeling presented in the Document.

Comments and Responses
8-hour REL

Comment #9:

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 #9:

The 8-hour REL is meant to protect offsite workers and children in schools. The chronic noncancer health impacts on those groups have been traditionally assessed with the 24-hour chronic RELs. Because offsite workers and children at school are generally exposed for 8 hours, the eight-hour RELs will ensure a more accurate assessment of the health impacts caused by their exposures.