# DRAFT Toluene HEAC Assessment and PEL Recommendation July 21, 2008

**Substance name:** Toluene

**CAS #**: 108-88-3 **Molecular weight**: 92.14

**Synonyms**: Benzene, methyl-; Methane, phenyl-; Methylbenzene; Methylbenzol; Phenylmethane; Toluol

**Molecular formula**: C7H8 **Structural formula**: 

**ppm to mg/m3 conversion at 25°C and 760 torr:** 1 ppm = 3.77 mg/m3; 1mg/m3 = 0.265 ppm

**Physical characteristics at room temperature**: At room temperature toluene is a clear-to-amber colorless liquid with an aromatic odor like benzene. The odor threshold is 2.5 ppm (9.6 mg/m3).

**Special physical characteristics**: Boiling point = 110.6°C. Vapor pressure = 59.3 torr at 40. Although it is a liquid at room temperature, toluene’s low vapor pressure results in extensive volatilization and it is present in workroom air as a vapor. Solubility in water at room temperature is 0.60 mg/ml. Solubility in nonpolar solvents is good.

Highly purified toluene contains less than 0.01% benzene, but crude grades can contain as much as 25% benzene. Commercial grades can also contain polynuclear aromatic hydrocarbons (PAHs) including pyrene, fluoranthene, and benzo[ghi]perylene.

**Flammability and other hazards**: Flash point = 4.40°C, closed cup. Flammability limits: lower 1.2%; upper 7.1%. Autoignition temperature: 480°C.

**Major commercial forms**: Based on a review of MSDSs, commercial forms include: liquids, aerosols, pastes, cartridges, and tubes (semisolid). See products and their toluene content below.

| **Product** | **Commercial Form** | **% Toluene** |
| --- | --- | --- |
| Glass Stain Clear  | Liquid | 39 |
| Rust Oleum Premium Metallic, Brilliant Metal Finish, Matte Aluminum  | Aerosol | 45 |
| Valvoline Carburetor and Choke Cleaner  | Liquid | 30-35 |
| Carpenters Goop Contact Adhesive and Sealant, Original Formula  | Tube | 37 |
| OSI Pro Series Formula #48 Construction Adhesive  | Cartridge | 5-10 |
| Plumbers Goop Contact Adhesive and Sealant, Original Formula  | Tube | 37 |
| Water White Rubbed Effect Clear Lacquer (Professional) | Aerosol | 19.5 |
| Parks Liquid Strip | Liquid | <40 |
| Titebond Fast Dry Contact Cement | Liquid | 50 |
| Color All Spray Enamel | Aerosol | 30-58 |

**Uses/Applications**: Toluene is widely used an octane booster in gasoline and as a solvent in paints, inks, lacquers, paint thinners, adhesives, fingernail polish, cleaning agents, and rubber. It is used to produce benzene, trinitrotoluene (TNT), nylon, plastics, and polyurethanes, and is often used as a substitute for benzene in many synthetic laboratory operations. Toluene is present in many household products including paints, thinners, rust inhibitors, and solvent-based cleaners.

## Current Occupational Exposure Limits (Time-weighted average or TWA)

| **Organization** | **TWA (ppm)** | **Notations/Other Information** |
| --- | --- | --- |
| Cal/OSHA | 5020 (proposed change) | SkinBased on visual impairment, female reproductive system, pregnancy loss (same as 2007 TLV) |
| OSHA  | 200 (current)100 (1989—vacated) | Same as 1968 TLVBased on hepatotoxicity, behavioral, and nervous system effects |
| NIOSH | 100(TWA = 10 hours)  | Central nervous system depression (NIOSH 1992) |
| American Conference of Governmental Industrial Hygienists (ACGIH) | 50 (1996-2006)20 (2007)  | Skin; A4\* Protect from subclinical changes in blue-yellow color vision and potential spontaneous abortion in female workers; A4BEI = 0.05 mg/L (toluene in blood);0.5 mg/L (o-cresol in urine); 1.6g/g creatinine (hippuric acid in urine)(ACGIH 2001)\*Not classifiable as a human carcinogen |
| Australia | 50 | Skin |
| Canada (Alberta, British Columbia, Quebec) | 50 | Skin |
| Belgium | 50 | Skin |
| Brazil | 78 | **---** |
| China | 13 | Skin |
| Czech Republic | 53 | Skin |
| EU - IOELV | 51 | Skin |
| Finland | 50 | Skin |
| Germany - MAK | 50 | Skin |
| Hong Kong | 50  | Skin |
| Ireland | 50 | Skin |
| Japan – JSOH | 50  | Skin |
| Malaysia | 50 | --- |
| Mexico | 50 | Skin; A4 |
| Netherlands | 40 | --- |
| New Zealand | 50 | Skin |
| Norway | 25 | Skin |
| Poland | 27 | Skin |
| South Africa – DOL RL | 50 | Skin |
| Spain | 50 | Skin |
| Sweden | 50 | Skin |
| United Kingdom | 50 | Skin; R63\*\*Possible risk of harm to the unborn child  |

## Organizational Sources and Recommendations

ACGIH Threshold Limit Value (TLV)

20 ppm TWA; A4

ACGIH TLV Documentation (2007)

## Findings/Conclusions

The Toluene TLV Documentation Summary states (in part):

A TLV-TWA of 20 ppm is recommended to protect against subclinical changes in blue-yellow color vision and the potential for spontaneous abortion in female workers. The National Toxicology Program (NTP) concluded that there was no evidence of carcinogenic activity in rats or mice inhaling up to 1200-ppm toluene for their lifetimes; therefore, an A4, Not Classifiable as a Human Carcinogen, notation is assigned to toluene. Based on the demonstration that toluene is poorly absorbed through the skin, a Skin notation is not warranted. There is no information upon which to assign a SEN notation or recommend a TLV-STEL.

There are several case reports of toluene abuse, and it has been documented to cause death, central nervous system (CNS) symptoms, and cardiac, renal, and hepatic toxicities, as well as fetal alcohol-like syndrome. Many epidemiology studies show a variety of effects in populations of rotogravure printers who were historically exposed to higher concentrations of toluene. These studies report neurobehavioral, color vision, reproductive, and developmental changes that are primarily related to cumulative exposures to toluene.

### Color Vision Impairment—TLV Basis

ACGIH cited two studies as the basis for the toluene TLV. A longitudinal study of rotogravure printers in France where personal air sampling in the breathing zone showed an average of 36 ppm toluene (**Campagna *et al*. 2001**), and a study of rubber production workers with an estimated exposure at the time of measurement of 42 ppm toluene (**Cavalleri *et al*. 2000**). The TLV of 20 ppm was recommended to protect against impairment of color vision based on the subclinical nature of the changes and the uncertainty about past exposure levels in the two studies.

1. **Campagna *et al.*, 2001** found a quantitative loss of color vision among male photogravure plant workers in a study conducted between 1991 and 1993 in France. Printers (N=72) had an average, current toluene exposure of 36 ppm [13–79 ppm]. Other workers (N=34) at the same plant had an ambient, current average toluene exposure of 8 ppm [4–20 ppm]. The latter group included engravers, forklift operators, compositors, and others not directly exposed to toluene. Non-exposed workers (N=19) from a bookbinding plant located in the same town served as a control group for the study. Eight-hour personal air sampling was performed during a workweek once in 1991 and once in 1992 at all workstations, during all shifts, and for almost all participants who worked at the printing plant, whether they were directly exposed or with ambient exposure. Historic exposure data from the last 30 years were used to construct cumulative exposure indices for toluene and hydrocarbons (aromatic naptha petroleum distillates containing toluene and xylene). Past cumulative exposure (ppm or mg/m3 x years) for the 72 printers was 346 ppm toluene [53–1602 ppm] and 1793 mg/m3 [200–21243 mg/m3] hydrocarbons. Past, cumulative, ambient exposures for the 34 non-printer plant workers were 80 ppm [9–482 ppm] for toluene, and 534 mg/m3 [31-4586 mg/m3] for hydrocarbons. The years of employment for exposed printers, workers with ambient exposure, and non-exposed workers were 18 [1-36], 19 [2-37], and 8 [1-35], respectively.

Color vision loss was assessed by the Lanthony D-15 desaturated panel (Lanthony 1978). Color vision loss was quantitatively established by the Color Confusion Index (CCI) and classified by type of acquired dyschromatopsia according to Verriest’s classification. A quantitative evaluation was performed by calculating the sum of the color differences of the caps adjacent to one another and the total color distance score using a previously developed formula. The CCI was calculated by dividing the participant’s total color distance score by a perfect score. The value 1 indicates a perfect score while higher values indicate color vision loss. CCIwas positively related to current airborne toluene levels and cumulative exposure indices for toluene and total hydrocarbon (**0.18** **< r < 0.35**). Odds ratios of acquired dyschromatopsia were significant for current airborne toluene, toluene, and total hydrocarbon past exposure (**1.27** [1.02-1.58], **1.21** [1.04-1.39], **1.15** [1.02-1.31])*,* respectively*.* The expected relationship between age and CCI was only observed for the best eye, not for the worst eye or the mean of both eyes. According to the authors, this suggests that the age effect was small compared to the exposure effect. The expected increase in chromatic confusion with alcohol consumption was not observed in the study—suggesting that the toxic effects of toluene on color vision hid the effect of alcohol consumption.

1. **Cavalleri *et al.*, 2000** studied the effect of toluene exposure on color vision of 33 rubber workers and 16 referents from another plant who were not exposed to toluene or other solvents. Toluene-exposed workers had a subclinical reduction in color vision compared with referents. The effect was related by the authors to solvent cumulative exposure—estimated as the product of urinary excretion of unmodified toluene by previous toluene exposure duration. This approach supports the hypothesis that impairment progresses as exposure continues. Urinary excretion of unmodified toluene was used to estimate toluene exposure in the rubber workers. The mean value of urinary toluene in the exposed workers was 63µg/l, which corresponds to an environmental level of 42 ppm.

The 33 workers in the study were exposed to toluene during rubber production. Twenty-four were involved in rubber smearing and nine used toluene in the preparation of solutions. The mean length of exposure to toluene was 117.3 months (standard deviation = 93), or 9.8 years. They were not significantly exposed to other chemicals that interfere with visual functioning. Preliminary environmental monitoring of other neurotoxic solvents (e.g., n-hexane, xylene, methyl isobutyl ketone, ethyl acetate) prior to the study indicated that they were below 1/100 of the current TLV-TWA. Exposure to these solvents was therefore considered not relevant. Age and smoking habits of exposed workers were not significantly different than the control group. Moderate alcohol consumption (< 50 gm/day) among the exposed workers, however, was significantly higher (*p*<0.01). Urine samples were collected at the end of the shift. As defined in the study, cumulative exposure = urinary toluene (µg/l) x exposure duration (months).

Color vision was assessed with the Lanthony 15 Hue desaturated panel (D-15 d) to ensure early detection of acquired dyschromatotopsia (Mergler and Blain 1987). As described above, it is based on the subject’s ability to recombine a set of 15 caps colored with desaturated colors in accordance with a definite chromatic sequence. The results were expressed quantitatively with the Color Confusion Index (CCI) and the Total Confusion Index (TOTCI). When the test is completed correctly, the “perfect” CCI is 1; errors increase the value. The greater the number and relevance of the mistakes, the higher the CCI. The TOTCI, like CCI, is a representation of the magnitude of the perceived color difference, but it is based on a different formula to quantify the perceptual distance between color caps included in the D-15 d. The authors compared the sensitivity of CCI and TOTCI to evaluate difference in color perception between exposed workers and referents.

The mean values of the **CCI** was increased significantly in toluene-exposed rubber workers compared to controls: **1.29 vs. 1.10,** respectively (p < 0.01), indicating that color perception was reduced in toluene-exposed workers.The mean **TOTCI** values for exposed workers and controls were **1.49** **vs. 1.16**, respectively (*p* < 0.001). Neither CCI nor TOTCI were correlated significantly with urinary levels of toluene. However, both CCI and TOTCI were correlated with cumulative dose (*r* = 0.505 [*p* = 0.003] and *r* = 0.586 [*p* = 0.0003], respectively. The correlation with cumulative dose suggests that there is a progressive loss of color vision with continuing exposure to toluene. The results of multivariate analysis showed no significant correlation between color vision loss and age, alcohol assumption, or cigarette smoking.

### Other Cited Color Vision Studies

#### Muttray *et al*. 1999

Eight male print shop workers did not show an impairment of color vision following acute exposure to pure toluene (297 to 362 ppm) for 28 to 41 minutes while cleaning containers. Color vision tests included the Lanthony desaturated d panel (D-15) test. Eight workers of a metalworking factory without any neurotoxic exposure, and tested according to the same procedure, served as controls. The small number of exposed workers limited the statistical power of the study.

#### Zavalic *et al*. 1998

Color vision impairment in workers exposed to a mean level of 132 ppm toluene was statistically significantly correlated with the level of toluene in air, toluene in blood, and orthocresol or hippuric acid in urine after the work shift. Color vision loss expressed as a Color Confusion Index (CCI) or Age and Alcohol intake-adjusted Color Confusion Index (AACCI) was examined in three groups of workers using the Lanthony-D-15 desaturated test. Group E1 consisted of 46 workers (43 women and 3 men) who glued shoe soles and were exposed to 32 ppm (11- 49 ppm) toluene throughout their working lives of 16± 6 years. Group E2 was comprised of 37 workers (34 men and 3 women) in a rotogravure printing exposed to 132 ppm (66 – 250 ppm) toluene for 18 ±6 years. Toluene had been used for the past 30 years in the printing inks and for manually rinsing the rollers without changes in technology, ventilation, etc. Group NE (non-exposed) consisted of 90 workers employed in two different factories. The NOAEL for toluene-induced effects on color vision impairment in the study was 32 ppm.

#### Muttray *et al.*, 1995

The authors found no effect of exposure to toluene during the workweek on the color vision of 59 rotogravure workers with a mean age of 36 (17-57 years) and a mean rotogravure employment time of 10 years (one month to 36 years). Testing was performed on Monday before shift and on Friday after shift. The color vision test battery included the Lanthony desaturated panel (D-15) test. The concentration of toluene in the blood of the exposed workers ranged from < 0.22 to 7.37 mg/l. Chronically-exposed workers were not compared to nonexposed controls.

#### Paramei *et al*., 2004

A meta-analysis of impairment of color vision caused by occupational exposure to toluene that was based on calculation of effect sizes reported in four studies did not show a common negative effect of toluene on color vision. The four studies included in the meta analysis were: Cavalleri *et al.* 2000, Muttary *et al.* 1999, Schäper *et al.* 2004, and Zavalic *et al.* 1998. Mean current toluene exposures (ppm) in the studies were 42, 50, 26, and 32, respectively. Potential reasons given by the authors for the results include: the low level of exposure, the use of “mean current” levels of exposure for the analysis (accumulating evidence indicates that cumulative and high past exposure are important), the limited number of studies included in the meta-analysis, and factors related to administration of the Lanthony D-15d test.

#### Nakatsuka *et al.*, 1992

The color vision of 63 men and 111 women was not affected by exposure to toluene (46 ppm, geometric mean). Lanthony’s new color test (Lanthony 1975) and Ishihara’s color vision test were used to measure color vision loss. The Lanthony’s new color test is not as sensitive as the D-15 d, and may explain the negative findings in this study compared to the Cavalleri *et al*. study. In addition, the outcomes of the tests in this study were evaluated qualitatively, instead of quantitatively (i.e., CCI and TOTCI were not used). Therefore, although the toluene exposures are comparable, a direct comparison with the results of Cavalleri *et al*. is not possible.

### Spontaneous Abortion —TLV Basis

ACGIH recommended a TLV of 20 ppm to protect against toluene-induced spontaneous abortions. The recommendation is based on a study by **Ng *et al.* 1992** in which the rate of spontaneous abortions was increased 2.8 times in women exposed to 88 ppm toluene compared to a community reference group. ACGIH also cited the study by **Roberts *et al.* 2003** as identifying no toluene-induced effects on fertility and reproductive performance in rats at 500 ppm. Developmental toxicity observed in this study at 2000 ppm was not cited as a basis for the TLV.

1. **Ng *et al.,* 1992** foundsignificantly higher rates for spontaneous abortions (**12.4/100 pregnancies**) among 55 married women (105 pregnancies) employed (5.7±3.2 years) in an audio speaker factory and exposed to high concentrations of toluene (mean 88, range 50-150 ppm) during final bond assembly processes that used large quantities of toluene-containing resinous glues. In comparison, the spontaneous abortion rate was **2.9/100 pregnancies** (*p=*0.025) among 31 women (68 pregnancies) with little or no toluene exposure (0-25 ppm) who worked in other departments in the same plant, and **4.5/100** **pregnancies** (*p*=0.005) among 190 community women (444 pregnancies) who underwent routine antenatal and postnatal care at public (governmental) maternal health clinics. There were a total of 13 spontaneous abortions in the high exposure group, two in the low exposure group, and 20 among the external or community group. Among the exposed women, significant differences were also noted in the rates of spontaneous abortion before employment in the factory (2.9 /100 pregnancies) and after employment (12.6/100 pregnancies).

The spontaneous abortion rate was defined as the number of spontaneous abortions divided by the number of pregnancies (including induced abortions). Rates of spontaneous abortions were determined using a reproductive questionnaire administered by personal interview. An examination of the distribution of classical risk factors for spontaneous abortion among the various comparison groups suggested little likelihood that the observed association was confounded by maternal age at pregnancy and order of gravidity. Few of the women smoked cigarettes or drank alcohol and race was not significantly associated with the risk of spontaneous abortions. Use of intrauterine devices for contraception prior to pregnancy also was not a factor. Four women in the high exposure group had repeated spontaneous abortions (one aborted three times, three aborted twice), and one woman in the maternal health clinics group aborted twice. Since the risk of spontaneous abortion is also influenced by the occurrence of previous abortions, a high rate of repeated abortions might account to some extent for the higher rates of spontaneous abortion among the highly exposed workers. Due to the small sample size, the authors were not able to restrict the analysis to only first pregnancies to eliminate this potential influence. Response bias and reporting bias may also have contributed to the study results.

1. **Roberts *et al.*, 2003** (also published as International Research and Development Corp., 1985) reported a toluene-induced inhibition of growth in F1 and F2 offspring at 2000 ppm in a two-generation rat reproductive toxicity study. Male and female rats were exposed to 0, 100, 500, and 2000 ppm toluene by whole body inhalation 6 hours/day, 7 days/week for 80 days pre-mating and 15 days of mating. Caesarean section of selected 2000 ppm (both sexes treated) dams at gestation day 20 showed reduced fetal body weight and skeletal variations. Toluene exposure did not have an adverse effect on fertility, reproductive performance, or maternal/pup behaviors during the lactation period in males and females of the parental or first generation. Exposure to toluene caused decreased pup weights throughout lactation in F1 and F2 2000 ppm (both sexes treated), and 2000 ppm (females only treated) groups. Exposure at 2000 ppm to male parents only did not cause similar weight decreases in offspring. The NOAEL for toluene-induced effects in the study was 500 ppm.

## Discussion and Assessment

The ACGIH Toluene TLV Documentation (ACGIH 2007) states that the toluene TLV of 20 ppm is recommended based on the subclinical nature of changes in color vision and uncertainty about past exposures in Campagna *et al*. 2001 and Cavalleri *et al*. 2000. However, the method used to derive a TLV of 20 ppm from the two studies is not presented.

The Campagna *et al*. 2001 and Cavalleri *et al*. 2000 studies identify LOAELs of 8 and 42 ppm toluene, respectively. In the Campagna *et al*. study, the mean current exposure of workers to ambient levels of toluene was 8 ppm, and the mean current exposure of printers who used toluene was 36 ppm. Both groups of workers in the study had significantly higher CCI values than the nonexposed group.

The study by Zavalic *et al.* 1998 (described above) identifies a NOAEL of 32 ppm and a LOAEL of 132 ppm. The Zavalic *et al*. study is cited by ACGIH, but was not identified as a basis for the TLV.

### PELs based on ACGIH-identified color vision impairment studies:

8 ppm (*study LOAEL*) ÷10 (LOAEL UF\*) ÷ 3 (Intraspecies UF\*\*) = **0.3 ppm** (Campagna *et al.* 2001)

36 ppm (*printers’ avg. current exposure*) ÷10 (LOAEL UF) ÷ 3 (Intraspecies UF) = **1 ppm** (Campagna *et al*. 2001)

42 ppm ÷10 (LOAEL UF) ÷ 3 (Intraspecies UF) = **1 ppm** (Cavalleri *et al*. 2000)

32 ppm ÷ 3 (Intraspecies UF) = **11 ppm** (Zavalic *et al.* 1998)

\*Based on OEHHA 2000 and OEHHA 2007.

\*\*Based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.”

The method ACGIH used to determine that the toluene TLV of 20 ppm protects against spontaneous abortion based on the cited studies (Ng *et al*. 1992 and Roberts *et al*. 2003) is not stated in the TLV Documentation. The Ng et al. study

identified a LOAEL of 88 ppm toluene. According to ACGIH, toluene did not induce adverse on fertility and reproductive performance at 500 ppm in the reproductive study in rats conducted by Roberts *et al*., 2003.

### PELs based on ACGIH-identified reproductive toxicity studies:

88 ppm ÷ 10 (LOAEL UF) ÷ 3 (intraspecies UF) = **3 ppm** (Ng *et al*. 1992)

500 ppm ÷ 3 (interspecies UF) ÷ 10 (intraspecies UF) = **17 ppm** (Roberts *et al.* 2003)

500 ppm ÷ 6 (interspecies UF★) ÷10 (intraspecies UF) = **8 ppm** (Roberts *et al.* 2003)

500 ppm ÷ 10 (interspecies UF★★) ÷ 10 (intraspecies UF) = **5 ppm** (Roberts *et al.* 2003)

(no adjustments were made for differences in occupational vs. experimental exposure and the faster breathing rate of

workers).

Due to the similarity in exposures, the experimental exposures to toluene used in the animal studies reviewed in the document were not adjusted to account for workplace exposures. This is consistent with OSHA (OSHA 1993).

Based on OEHHA 2000 and OEHHA 2007.

★Based on OEHHA 2008. In the current, draft risk assessment guidelines for deriving noncancer reference exposure levels, the interspecies UF is increased from 3 to 6.

★★Based on OSHA 1993. In the noncancer risk assessment for glycol ethers, OSHA applied an interspecies UF of 10.

 Based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.”

Based on above explanation () and on protecting the developing fetus upon which, according to OSHA, the “healthy worker effect” is not necessarily conferred (OSHA 1993).

## Organizational Sources and Recommendations (continued)

US EPA Inhalation Reference Concentration (RfC)

5 mg/m3 (1 ppm)

2005

Toxicological Review of Toluene

In Support of Summary Information on the Integrated Risk Information System (IRIS)

## Findings/Conclusions

Based on a review of a substantial database of toluene effects in occupationally-exposed humans, EPA concluded that the weight of evidence from these studies indicates neurologic effects (i.e., impaired color vision, impaired hearing, decreased performance in neurobehavioral analysis, changes in motor and sensory nerve conduction velocity, headache, and dizziness) as the most sensitive endpoint. According to EPA, none of the toluene-induced adverse health effects reported in the available human studies occurred at doses lower than those observed for neurological effects. Although animal studies

(NTP 1990) have also suggested respiratory irritation as a sensitive effect, irritation in humans appears to occur at higher exposure concentrations than those resulting in neurologic effects.

### Occupational Neurological Studies—RfC Basis

EPA considered all of the available occupational studies for the principal study upon which to base the derivation of the RfC. Numerous human studies have identified NOAELs in the range of 25-50 ppm toluene for individual neurological effects. No single study stood out as the best study on which to characterize neurological effects or to specify a single critical effect. As a result, EPA considered ten studies as adequate. The determination of study adequacy was based on use of accepted testing procedures for neurological endpoints, chronic exposure duration, inclusion of a measure of exposure, comparison to defined control groups, and no known co-exposure to other solvents in the workplace.

Partial summary of information on the 10 studies EPA used in deriving the toluene RfC. See US EPA 2005 for complete information.

| **No.** | **Study** | **NOAEL****(ppm)** | **LOAEL****(ppm)** | **Effect/Test** | **Noted Potential Limitations** |
| --- | --- | --- | --- | --- | --- |
| 1 | Abbate et al., 1993 | None | 97 | Brainstem response Auditory-evoked potential |  |
| 2 | Boey et al., 1997 | None | 91 | Neurophychological examination; digit span, visual reproduction, Benton visual retention test, trail making test, symbol digit modality test, grooved pegboard test, and finger tapping tests  | Control workers were exposed to 12 ppm toluene |
| 3 | Cavalleri et al., 2000 | None | 42 | Color vision impairment(Lanthony D-15) | Exposure measured from urinary excretion of toluene: on basis of previous data, air concentrations estimated to be 42 ppm. |
| 4 |  Eller et al., 1999 | 20 | >100 | Neuropsychological examination (Cognitive Function Scanner); verbal and nonverbal learning and memory, visumotor function, computerized neurological exam (CATSYS, TREMOR, and SWAY), subjective assessment | The high exposure classification was based on historical exposures which may have exceeded 100 ppm for up to 27 years. |
| 5 | Foo et al., 1990 | None | 88 | Neurobehavioral tests: Benton visual retention test, visual reproduction, trail making, grooved pegboard, digit span, digit symbol, finger tapping, and simple reaction time | Control workers were exposed to 13 ppm toluene for 2.5±3.2 years. The education level was lower in the exposed group. As a result, data from the neurobehavioral tests were adjusted for years of education using a generalized linear model. |
| 6 | Murata et al., 1993 | None | 83 | Electrophysiological analysis of maximal motor and sensory nerve conduction velocity (MCV & SCV) | Exposed workers were matched for age but not for alcohol consumption |
| 7 | Nakatsuka et al., 1992 | 44-48 | None | Color vision impairment (Lanthony’s new color test and Ishihara’ color vision test) | In lieu of determining exposure duration, groups were age-matched to control for effects on aging on color vision. |
| 8 | Neubert et al., 2001 | 39 (exp grp 1) | 81 (exp grp IV) | Psychophysiological and psychomotor testing: verbal memory span, visumotor performance, immediate visual memory, self-rating of feeling, biosensory vigilance, critical flicker fusion frequency test, personality dispositions | Exposure was identified as chronic but the duration was not reported |
| 9 | Vrca et al., 1995 | None | 40-60 | Visual evoked potentials | Exposure levels were estimated based on urinary levels of metabolites and toluene in blood |
| 10 | Zavalic et al., 1998a | 32 | 132 | Color vision impairment(Lanthony D-15) | The results were reported in several publications (Zavalic et al., 1998a,b,c); some reporting discrepancies exist regarding the number of workers in the exposed and control groups and the statistical analyses. |

Campagna *et al*. 2001, one of the studies cited as the basis for the toluene TLV, was not considered adequate for deriving the RfC because of the known co-exposure to other solvents among workers in the study (US EPA 2005).

### NOAEL—Occupational Neurological Studies

EPA used the ten studies summarized above to determine a point of departure. The studies were weighted equally since it was determined that none was clearly a stronger study. The highest NOAEL was identified as 44 ppm (Nakatsuka *et al*., 1992). The lowest LOAELs were determined as 40-42 ppm (Vcra *et al*., 1995, 1997; Cavalleri *et al*., 2000). An arithmetic mean of the NOAEL values in the ten selected studies was chosen to represent an average point of departure.

EPA used the average exposure level of **34 ppm** as the point of departure for the derivation of the RfC. This value is lower than the LOAELs of 40-42 ppm. The range of NOAELs for the studies is 20-48 ppm.

## Discussion and Assessment

EPA acknowledged that there is some uncertainty in using an average value from a suite of studies with varied endpoints and varied levels of response for the point of departure. However, the agency concluded that the uncertainty is expected to be less than that associated with choosing any particular one of the available studies for deriving the point of departure since there were potential limitations associated with many of the available studies and no single study stands out as being

of the highest quality. In addition, EPA explained that the subset of ten studies presents a cluster of NOAELs for neurological effects which are generally below reported LOAELs for all endpoints.

### PEL based on the average NOAEL from the occupational neurological studies identified by EPA

34 ppm ÷ 3 (Intraspecies UF\*) = **11 ppm**

\*Based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.” Application of a UF is appropriate since none of the studies were considered by EPA to be strong, and the average NOAEL of 34 ppm for the studies is close to and not substantially different than the LOAELs of 40-42 ppm.

## Organizational Sources and Recommendations (continued)

Cal/EPA OEHHA

Chronic Reference Exposure Level (cREL)

300 µg/m3 (0.07 ppm)

**Critical effect**: Neurotoxic effects (decreased brain [subcortical limbic area] weight, altered dopamine receptor binding)

available: <http://www.oehha.ca.gov/air/chronic_rel/pdf/108883.pdf>

## Findings/Conclusions

A NOAEL of 40 ppm identified from a rat inhalation study (**Hillefors-Berglund *et al*. 1995**) was used to derive the cREL. The study also identified a LOAEL of 80 ppm. Additional studies (Orbaek and Nise, 1989 and Foo *et al*., 1990) provided support for the cREL.

Inhalation exposure of male rats to 80 ppm toluene decreased the wet weight of the caudate-putamen in the subcortical limbic area, and lead to persistent increases in the affinity of dopamine D2 agonist binding in the caudate putamen. The effects were specific to toluene, and were not caused by similar exposures to xylene and styrene. Toluene exposure also did not significantly affect either the body weights, the wet weights of the whole brain, serum prolactin levels, and other aspects of binding to the caudate putamen.

OEHHA points out that the adverse neurotoxic effects associated with toluene exposure in the Hillefors-Berglund *et al*. study occur in areas of the rat brain that are structurally and functionally similar to the brain areas (basal ganglia, thalami) of some human toluene abusers that demonstrate MRI alterations (T2 hypointensity). The altered MRI parameters may be the result of the partitioning of toluene into the lipid membranes of brain cells (Ungar *et al*., 1994).

OEHHA also used a LOAEL of 88 ppm toluene identified in a supportive human study (**Foo et al. 1990**) to derive a cREL of 0.1 ppm for toluene. The results of neurobehavioral tests administered to 30 female electronic assembly workers exposed to 88 ppm toluene showed statistically different results compared to the test results of 30 matched control workers exposed to 13 ppm toluene. The tests measured manual dexterity (grooved peg board), visual scanning (trail making, visual reproduction, Benton visual retention, and digit symbol), and verbal memory.

## Discussion and Assessment

The cREL document states that OEHHA prefers to use human data if both human and animal adverse effect data on a chemical are available. However, although human neurotoxicity data on toluene are available and support derivation of the toluene REL, the Hillefors-Berglund *et al.* study provides data which are specific and sensitive measures of neurotoxicity

that would not be obtainable in human studies. In addition, OEHHA points out that the Hillefors-Berglund *et al*. study has better exposure characterization than the human occupational exposure studies. However, the availability of human studies with generally consistent effects allowed OEHHA to reduce the interspecies UF from 3 to 1 in the cREL derivation based on Hillefors-Berglund *et al*.

### PEL based on neurotoxicity studies used by OEHHA to derive the toluene cREL

40 ppm ÷ 10 (Subchronic UF**§**) ÷ 1 (Interspecies UF**§§**) ÷ 3 (Intraspecies UF**§§§**) = **1 ppm** (Hillefors-Berglund *et al*., 1995)

88 ppm ÷10 (LOAEL UF**§**) ÷ 3 (Subchronic UF**§§**) ÷ 3 (Intraspecies UF**§§§**) = **1 ppm** (Foo *et al*., 1990)

**§**Based on OEHHA 2000 and OEHHA 2007

**§§**Based onOEHHA 2000b

**§§§** Based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.”

## Organizational Sources and Recommendations (continued)

Cal/EPA OEHHA

Maximum Allowable Dose Limit (MADL) for Reproductive (Developmental) Toxicity

13 mg/d (inhalation)

Donald *et al*. 1991

## Findings /Conclusions

OEHHA used a NOAEL of 500 ppm toluene identified in a rat inhalation study

(International Research and Development Corporation, 1985) to derive the toluene inhalation MADL. The study, subsequently published as **Roberts et al. 2003**, is summarized above under the ACGIH TLV section.

### Other Relevant Developmental Studies

**Roberts *et al*, 2007** reported a reduction inmean fetal weights at 1500 ppm toluene when pregnant rats were exposed via whole body inhalation to 0, 750, 1500 and 3000 ppm toluene 6 hours/day from gestation day (GD) 6-15 inclusive. Doses were selected from a preliminary study performed over a range of concentrations from 0 to 5000 ppm, in which maternal and fetal toxicity were observed at 2000 ppm and above. Caesarean section on G20 showed no adverse effects on implantation, number and viability of fetuses, or fetal sex distribution. Extensive statistical analysis of fetal body weight data supported the conclusion that there is no toxicologically significant dose-related effect on fetal body weight at or below 750 ppm toluene. The NOAEL for developmental toxicity was 750 ppm toluene.

**Saillenfait *et al*., 2007** found a significant reduction in fetal weight associated with exposure to 1500 ppm toluene following whole body inhalation exposure of rats to 0, 500, and 1500 ppm toluene 6 hours/day, from day 6 to day 20 of gestation. No embryolethal or teratogenic effects were observed at any exposure. The NOAEL toluene-induced developmental toxicity in the study was 500 ppm.

## Discussion and Assessment

### PEL based on NOAELs identified in developmental toxicity studies

500 ppm ÷ 3 (interspecies UF) ÷ 10 (intraspecies UF) = **17 ppm** (Roberts *et al.* 2003; Saillenfait et al. 2007)

500 ppm ÷ 6 (interspecies UF★) ÷10 (intraspecies UF) = **8 ppm** (Roberts *et al.* 2003; Saillenfait et al. 2007)

500 ppm ÷ 10 (interspecies UF★★) ÷ 10 (intraspecies UF) = **5 ppm** (Roberts *et al.* 2003; Saillenfait et al. 2007)

750 ppm ÷ 3 (interspecies UF) ÷ 10 (intraspecies UF) = **25 ppm** (Roberts *et al.* 2007)

750 ppm ÷ 6 (interspecies UF★) ÷10 (intraspecies UF) = **12.5 ppm** (Roberts *et al.* 2007)

750ppm ÷ 10 (interspecies UF★★) ÷ 10 (intraspecies UF) = **7**.**5 ppm** (Roberts *et al.* 2007)

 (no adjustments were made for differences in occupational vs. experimental exposure and the faster breathing rate of workers).

Based on OEHHA 2000 and OEHHA 2007.

★Based on OEHHA 2008. In the current, draft risk assessment guidelines for deriving noncancer reference exposure levels, the interspecies UF is increased from 3 to 6.

★★Based on OSHA 1993. In the noncancer risk assessment for glycol ethers, OSHA applied an interspecies UF of 10.

 Based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.”

Based on above explanation () and on protecting the developing fetus upon which, according to OSHA, the “healthy worker effect” is not necessarily conferred (OSHA 1993).

## Summary of Derived PELs

| **Study** | **Type** | **Health Endpoint** | **LOAEL (ppm)** | **NOAEL (ppm)** | **UF (Total)** | **PEL (ppm)** |
| --- | --- | --- | --- | --- | --- | --- |
| Campagna et al. 2001 | Occup. | Color vision loss | 8 | --- | 3010 LOAEL; 3 intraspecies | **0.3** |
| Campagna et al 2001 | “ “ | “ “ | 36 (avg. exposure) | --- | 3010 LOAEL; 3 intraspecies | **1** |
|  |  |  |  |  |  |  |
| Cavalleri et al. 2000 | Occup. | Color vision loss | 42 | --- | 3010 LOAEL; 3 intraspecies | **1** |
| Zavalic et al. 1998a | Occup. | Color vision loss | 132 | 32 | 3 intraspecies | **11** |
| Ng et al. 1992 | Occup. | Spontaneous Abortion | 88 | --- | 3010 LOAEL; 3 intraspecies | **3** |
| Roberts et al. 2003Saillenfait et al. 2007 | Rat inhal. | Reproductive Developmental  | 20001500 | 500 | 303 interspecies; 10 intraspecies | **17** |
| Roberts et al. 2003Saillenfait et al. 2007 | Rat Inhal. | Reproductive Developmental | 20001500 | 500 | 606 interspecies; 10 intraspecies | **8** |
| Roberts et al. 2003Saillenfait et al. 2007 | Rat Inhal. | Reproductive Developmental | 20001500 | 500 | 10010 interspecies; 10 intraspecies | **5** |
| Roberts et al. 2007 | Rat inhal. | Developmental  | 1500 | 750 | 303 interspecies; 10 intraspecies | **25** |
| Roberts et al. 2007 | Rat inhal. | Developmental | 1500 | 750 | 606 interspecies; 10 intraspecies | **12.5** |
| Roberts et al. 2007 | Rat inhal. | Developmental | 1500 | 750 | 10010 interspecies; 10 intraspecies | **7.5** |
| Suite of 10 studies  | Occup. | Various neurological(color vision, etc,) | 40-42 | 34 avg.(20-48) | 3 intraspecies | **11** |
| Hillefors-Berglund et al. 1995 | Rat inhal. | Neurological | 80 | 40 | 3010 subchronic; 3 intraspecies | **1** |
| Foo et al. 1990 | Occup. | Neurological | 88 | --- | 9010 LOAEL; 3 subchronic;3 intraspecies | **1** |

## HEAC Health-Based Assessment and Toluene PEL Recommendation

A PEL of **11 ppm TWA** is recommended to protect workers from toluene-induced neurologic effects (i.e., impaired color vision, impaired hearing, decreased performance in neurobehavioral analysis, changes in motor and sensory nerve conduction velocity, headache, and dizziness).

The PEL recommendation is based on the **average NOAEL of 34 ppm** identified by US EPA from ten occupational neurotoxicity studies (US EPA 2005). The HEAC assessment, consistent with EPA’s evaluation, is based on the conclusion that neurologic effects are the most sensitive endpoint of occupational exposure to toluene, and that no single study stood out as the best study upon which to specify a critical neurological effect. An intraspecies uncertainty factor of 3 was applied to the NOAEL based on differences in worker susceptibility to toluene exposure due to the inability of certain populations to metabolize toluene (Kawamoto *et al*. 1994), and the effects of age (Ruddock 1965; Bowman *et al*. 1984) and diabetes (Hardy *et al*. 1992; Utku and Atmaca 1992; Mäntyjärvi 1992) on color vision impairment caused by toluene. Application of a UF to the NOAEL of an occupational study is consistent with OSHA (1989) in which OSHA states: “…*if the available data include a NOEL derived from a well-conducted human study, a smaller safety factor might be used to establish an exposure limit than would be used if the data to be used to establish the limit consisted of a NOEL from an animal study; in the latter case, there is greater uncertainty regarding the relationship between the animal NOEL and human NOEL. Safety factors have also been used to recognize the fact that the human population is heterogeneous and that there may be a wide variation in individual responses to toxic substances (the wide range in the odor thresholds reported for some substances is a good illustration of individual variability in response)*.” Application of a UF is appropriate since none of the studies were considered by EPA to be strong, and the average NOAEL of 34 ppm for the studies is close to and not substantially different than the LOAELs of 40-42 ppm. Justification for using the 1989 OSHA reference to support use of an uncertainty factor for an occupational study is provided by a US General Accounting Office report on chemical risk assessment at OSHA (US GAO 2001). The report points out that OSHA currently has no formal internal risk assessment guidance. Instead, the GAO states that OSHA has primarily described its general risk assessment methods, as well as the rationale for specific models and assumptions selected, in the record of each risk assessment and regulatory action.

As shown in the PEL summary table, the recommended PEL for toluene is consistent with the 11 ppm PEL based on color vision impairment derived from the study by Zavalic et al*.*, 1998. However, it is significantly higher than the 0.3 and 1 ppm PELs derived from three other neurologic studies in the table—Campagna et al., 2001; Cavalleri et al., 2000; and Foo et al., 1990, respectively. The Zavalic et al., Cavalleri et al., and Foo et al., studies were among the ten studies EPA used to calculate the average NOAEL, which is the basis for the HEAC recommendation. EPA did not select Campagna et al. 2001 because of co-exposure to hydrocarbons reported by the authors. In contrast, Campagna et al. 2001 is one of the studies cited by ACGIH as the basis for the toluene TLV. The recommended PEL is also ten times higher than the 1 ppm PEL derived from the Hillefors-Berglund et al. 1995 study, which is the basis for the OEHHA chronic REL for toluene. The study provides important support for neurologic effects as an early and sensitive endpoint of toluene-induced adverse health effects in workers, however it did not stand out as the best study upon which to derive the recommended PEL given the availability of occupational neurologic studies from which comparable PELs could be derived, and lack of clarity regarding how the toluene-induced neurologic effects in rats would be manifested in humans.

The recommended PEL may also protect against the developmental toxicity of toluene reported in the studies by Roberts et al., 2003 and 2007, and Saillenfait et al., 2007, depending on the application of uncertainty factors. However, it will not protect against toluene-induced spontaneous abortions reported in the study by Ng et al., 1992 since it is higher than the PEL of 3 ppm derived from this study. The recommended PEL of 11 ppm is lower than the ACGIH TLV of 20 ppm, which is based on protecting against color vision impairment and spontaneous abortion. The scientific rationale for the derivation of the 20 ppm TLV could not be determined based on the studies cited by ACGIH (Campagna et al. 2001, Cavalleri et al. 2000, and Ng et al. 1992) and on other information presented in the Toluene TLV Documentation (ACGIH 2007).

## Production/Import & Facility Usage/Release Information

* Major US producers include**:**

 BP Chemicals, Texas; Chalmette Refining, LA; Exxon Mobil, LA and Texas; Flint Hills Resources, Texas;

 Clark Refining & Marketing, OH; Sunoco, Penn; Chevron Chemical, Texas

Available: <http://www.the-innovation-group.com/ChemProfiles/Toluene.htm>

* Major California industrial sectors (2-digit SIC with 2002 reported total environmental releases (Scorecard 2007)

| **Rank** | **Industrial Sector**  | **Toluene (Pounds)** |
| --- | --- | --- |
| 1 | Petroleum and coal products | 137,631 |
| 2 | Transportation equipment |  95.895 |
| 3 | Chemicals and allied products |  72,910 |
| 4  | Rubber & misc. plastic products |  36,219 |
| 5 | Wholesale trade—nondurable goods |  30,049 |
| 6 | Paper and allied products |  27,150 |
| 7 | Primary metal industries |  18,543 |
| 8 | Fabricated metal products |  10,404 |
| 9 | Furniture and fixtures |  10,184 |
| 10  | Electronic & other electric equipment |  1,685 |
| 11 | Misc. manufacturing industries |  1,260 |

MajorCalifornia facilities with reported total environmental releases in 2002 (Scorecard 2007)

 (Total = 99 ranked facilities)

| **Rank** | **Facility** | **Toluene (Pounds)**  |
| --- | --- | --- |
| 1 | New United Motor Mfg. Inc, Fremont | 35,250 |
| 2 | Fabri Cote, Los Angeles | 34,120 |
| 3 | Chevron Prods. Co., Richmond | 32,032 |
| 4 | Fleetwood Motor Homes of CA Inc., Riverside | 26,615 |
| 5 | Johnson Laminating & Coating Inc., Carson | 26,344 |
| 6 | 3M, Monrovia | 19,500 |
| 7 | Western Tube & Conduit Corp., Carson | 18,000 |
| 8 | Truck Accessories Group (DBA Leer West), Woodland | 17,002 |
| 9 | Valero Refining Co. California Benicia Refy., Benicia | 15,100 |
| 10 | Exxon Mobil Oil Corp., Torrance Refy., Torrance | 14,203 |
| 11 | Conoco Phillips S.F. Refy., Rodeo | 14,008 |
| 12  | Northrop Grumman Corp., El Segundo | 13,796 |
| 13 | Tesoro Refining & Marketing Co., Martinez | 12.798 |
| 14 | Shell Oil Prods. U.S. Martinez Refy., Martinez | 12,400 |

## Measurement Information

### Air Monitoring

OSHA Method # 111: Adsorbent tube samples are collected by drawing workplace air through either coconut shell charcoal or Anasorb® 747 tubes with personal sampling pumps. Diffusive samples are collected by exposing eiter 3M 3520 Organic Vapor Monitors (OVMs) or SKC 575-002 Passive Samplers to workplace air. Samples are desorbed with 60/40 (v/v) *N,N*-dimethylformamide/carbon disulfide (DMF/CS2) and analyzed by gas chromatography using a flame ionization detector.

Reliable quantitation limit (240-min samples): **18.1 ppb** or 63.3 µg/m3 (charcoal tubes) ; **25.4 ppb** or 95.5 µg/m3 (Anasorb® 747 tubes) (OSHA 2007)

Available: <http://www.osha.gov/dts/sltc/methods/organic/org111/org111.html> (accessed 5/1/08)

### Biological Monitoring

ACGIH Toluene Biological Exposure Index (BEI) Information

| **Determinant** | **Sampling Time** | **BEI** |
| --- | --- | --- |
| o-Cresol in urine | End of shift | 0.5 mg/L |
| Hippuric acid in urine | End of shift | 1.6 g/g creatinine |
| Toluene in blood | Prior to last shift of workweek | 0.05 mg/L |

See ACGIH Toluene BEI Documentation (ACGIH 2001) for specific measurement information.

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