CHRONIC TOXICITY SUMMARY

TOLUENE

(Methyl benzene; methyl benzol; phenyl methane; toluol)

CAS Registry Number: 108-88-3

I. Chronic Toxicity Summary

Inhalation reference exposure level

300 µg/m³ (70 ppb)

Critical effect(s)

Neurotoxic effects (decreased brain [subcortical limbic area] weight, altered dopamine receptor binding).

Hazard index target(s)

Nervous system; respiratory system; teratogenicity

II. Physical and Chemical Properties (HSDB (1999) except as noted)

Description

Colorless liquid

Molecular formula

C₇H₈

Molecular weight

92.13 g/mol

Density

0.8661 g/cm³ @ 20°C

Boiling point

110.6 °C (CRC, 1994)

Melting point

−94.9° C (CRC, 1994)

Vapor pressure

28.1 torr @ 25°C (U.S. EPA, 1984)

Solubility

miscible in most organic solvents

Conversion factor

1 ppm = 3.76 mg/m³ @ 25°C

III. Major Uses or Sources

Toluene occurs naturally as a component of crude oil and is produced in petroleum refining and coke oven operations; toluene is a major aromatic constituent of gasoline (HSDB, 1999). It is used in household aerosols, nail polish, paints and paint thinners, lacquers, rust inhibitor, adhesives and solvent based cleaning agents. Toluene is also utilized in printing operations, leather tanning and chemical processes. Benzene and other polycyclic aromatic hydrocarbons are common contaminants of toluene. Toluene is considered a sentinel chemical for benzene in the context of air and water sample monitoring. In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of toluene was approximately 2.2 ppb. For 1998, annual statewide industrial emissions of toluene from facilities reporting under the requirements of the Air Toxics Hot Spots Act in California were estimated to be 5,176,626 pounds (CARB, 1999). Note that this estimate is for stationary sources, and does not include emissions from mobile sources.

IV. Effects of Human Exposures

Neurological Effects

Most studies reporting adverse effects due to chronic toluene exposures involve either toluene-containing solvent abuse or occupational exposure to toluene. Solvent abusers are generally exposed to higher levels of toluene than are workers. A continuum of neurotoxic effects ranging from frank brain damage to degraded performance on psychometric tests which roughly track exposure levels has been observed.
Chronic toluene abuse has been shown to cause permanent changes in brain structure (loss of grey and white matter differentiation; cerebral, cerebellar and brainstem atrophy) which correlated with brain dysfunction as measured by magnetic resonance imaging (MRI) and brainstem auditory evoked response (BAER) evaluations (Caldemeyer et al., 1996; Filley et al., 1990; Ikeda and Tsukagoshi, 1990; Rosenberg et al., 1988a; Rosenberg et al., 1988b; Yamanouchi et al., 1995; reviewed by Agency for Toxic Substances and Disease Registry (ATSDR), 1999).

Eleven chronic solvent (spray lacquer; ≈ 60% toluene, 10% dichloromethane) abusers were examined using MRI and BAER tests (Rosenberg et al., 1988b). Neurological abnormalities were seen in four of 11 subjects and included brainstem, cerebellar, cognitive and pyramidal findings. Brain MRIs were abnormal in three of 11 subjects and indicated the occurrence of diffuse cerebral, cerebellar, and brainstem atrophy and loss of differentiation between the gray and white matter throughout the CNS. BAERs were abnormal in five of 11 individuals. All three individuals with abnormal MRI scans also had abnormal neurological examinations and BAERs. However, two of five individuals with abnormal BAERs had normal neurological examinations and MRI scans. The authors suggested that BAERs may detect early CNS injury from toluene inhalation, even at a time when neurological examination and MRI scans are normal.

Two subjects of a group of 22 hospitalized solvent abusers (primarily abusing toluene-based solvents) demonstrated decreases in intelligence quotient (IQ) as measured by the comparison of tests administered before the commencement of solvent abuse with tests administered during hospitalization for long-term solvent abuse (Byrne et al., 1991).

Filley et al. (1990) studied 14 chronic toluene abusers using MRI and neuropsychological evaluations. The neuropsychological testing indicated that three patients functioned normally, three were in a borderline range, and eight were impaired. Independent analyses of white matter changes on MRI demonstrated that the degree of white matter abnormality was strongly correlated (p < 0.01) with neuropsychological impairment. The authors concluded that dementia in toluene abuse appears to be related to the severity of cerebral white matter involvement.

Six chronic toluene abusers were examined using MRI by Caldemeyer et al. (1996). All patients examined demonstrated white matter atrophy and T2 hyperintensity (T2: “Spin-spin” relaxation time; a time constant that reflects the rate at which protons stop rotating in phase with each other because of the local magnetic fields of adjacent nuclei; OTA, 1984), and five of six demonstrated T2 hypointensity of the basal ganglia and thalami. The authors noted a correlation between the severity of white matter degeneration and degree of neurological dysfunction. However, there was no correlation between the severity of imaged white matter changes and the presence of T2 hypointensity or duration of toluene abuse. Additionally, no definite clinical evidence of damage to the basal ganglia and thalamus was found despite the MR imaging finding of T2 hypointensity..

Ungar et al. (1994) developed a physical bilayered model of dipalmitoylphosphatidylcholine (DPPC) and toluene, and subjected DPPC control and toluene-mixed bilayers to MRI. T1 (T1: “Spin-lattice” relaxation time; a time constant that reflects the rate at which excited protons exchange energy with the surrounding environment; OTA, 1984) and T2 were measured as a function of toluene and lipid concentrations. Measurements of the DPPC-toluene model indicated that toluene-containing lipid bilayers substantially shortened T2 and had little effect on T1. By comparison, DPPC alone had little effect on either T1 or T2. The authors believe that these results suggest that partitioning of toluene into the lipid membranes of cells in cerebral tissue may be responsible for the hypointensity of basal ganglia noted on T2-weighted MR images of brains of toluene abusers.

**Occupational exposure**
Solvent workers exposed to 42.8 ppm toluene (estimated as a time-weighted average) for an average duration of 6.8 years reported a significantly greater incidence of sore throat, dizziness and headache than controls; the sore throat and headache incidence demonstrated a rough dose-response (Yin et al., 1987).

Orbaek and Nise (1989) examined the neurological effects of toluene on 30 rotogravure printers, 33-61 years of age (mean 50), employed at two Swedish printing shops for 4-43 years (median 29) in 1985. Mean exposure levels at the two printing shops were 43 and 157 mg/m$^3$ of toluene, respectively; however, before 1980 the exposure levels had exceeded 300 mg/m$^3$ in both shops. The authors noted that rotogravure printing provides an occupational setting with practically pure toluene exposure. Comparisons were made to a reference group of 72 men aged 27-69 (mean 47). The alcohol consumption of both the workers and referents was also determined (< 200 g/week or > 200 g/week). Neurological function in the workers and referents was evaluated using interviews and psychometric testing; the results from each of the two printing shops were pooled. The printers reported statistically significantly higher occurrences of fatigue (60%), recent short-term memory problems (60%), concentration difficulties (40%), mood lability (27%), and other neurasthenic symptoms. The printers also scored significantly worse than referents in a number of psychometric tests, including synonym, Benton revised visual retention and digit symbol tests, even after adjustment for age. For all comparisons, tests of interaction between the effects of toluene exposure and alcohol consumption were not statistically significant.

A battery of neurobehavioral tests was performed in 30 female workers exposed to toluene vapors in an electronic assembly plant (Foo et al., 1990). The average number of years worked was 5.7 ± 3.2 for the exposed group and 2.5 ± 2.7 years for the controls. Study subjects did not smoke tobacco or drink alcohol, were not taking any medications, and had no prior history of central or peripheral nervous system illness or psychiatric disorders. The exposed group of workers inhaled a time-weighted average (TWA) of 88 ppm (330 mg/m$^3$) toluene while the control workers inhaled 13 ppm (49 mg/m$^3$). A significant decrease in neurobehavioral performance was observed in the exposed workers in 6 out of 8 tests. Irritant effects were not examined, and concurrent exposures to other chemicals were not addressed. In this study, 88 ppm was considered a LOAEL for central nervous system effects. However, the workers designated by the authors to be controls did not comprise a true control group, since they were exposed to 13 ppm toluene. This may have resulted in an underestimation of the effects of exposure to 88 ppm toluene. Similar effects were noted in a follow-up study by Boey et al. (1997).

Abbate et al. (1993) evaluated alterations induced in the auditory nervous system by exposure to toluene in a group of rotogravure workers. A sample of 40 workers of normal hearing ability was selected from a group of 300 workers who were apparently in good health but were professionally exposed to toluene (12 – 14 years exposure, 97 ppm average exposure, exposure assessment not described). They were subjected to an adaptation test utilizing a BAER technique with 11 and 90 stimulus repetitions a second. The results were compared with an age and sex-matched control group not professionally exposed to solvents. A statistically significant alteration in the BAER results was noted in the toluene-exposed workers with both 11 and 90 stimuli repetitions. The authors suggested that these results can be explained as a toluene-induced effect on physiologic stimulus conduction mechanisms, even in the absence of any clinical sign of neuropathy. Furthermore, this effect could be observed in the responses of the entire auditory system, from peripheral receptors to brainstem nuclei.

A group of 49 printing-press workers occupationally exposed to toluene for approximately 21.6 years was studied by Vrca et al. (1997). Toluene exposure levels were determined from blood toluene and urinary hippuric acid levels, and were estimated to range from 40-60 ppm. No control group was used. Brain evoked auditory potential (BEAP; similar to BAER) and visual evoked potential (VEP) measurements were performed on a Monday morning after a nonworking weekend. There was a significant increase in the latencies of all the BEAP waves examined, except for P2 waves, as well as in the interpeak latency (IPL) P3-P4, while IPL P4-P5 decreased significantly with the length of exposure. No correlation was noted between the amplitude of BEAP waves and the length of exposure. The amplitude but not the latency of all the VEPs examined decreased significantly with the length of exposure.

The effects of acute and chronic toluene exposure on color vision were studied in a group of eight rotogravure printing workers (Muttray et al., 1999). The workers had been employed as printers for an
average of 9.8 years. The color vision acuity of the workers before and after an acute toluene exposure (28 – 41 minutes in duration, concentration 1115 – 1358 mg/m$^3$) was evaluated using the Farnsworth panel D-15 test, the Lanthony desaturated panel D-15 test, and the Standard Pseudoisochromatic Plates part 2. A control group of 8 unexposed workers was also tested. Acute toluene exposure had no effect on color vision. Print worker performance prior to acute toluene exposure (chronic effects) was similar to controls on the Farnsworth panel D-15 and Standard Pseudoisochromatic Plates part 2 tests. Print worker performance on the Lanthony desaturated panel D-15 test was worse than that of controls (median scores of 1.18 and 1.05 for exposed and controls (higher number indicates degraded performance), respectively, but not significantly ($p = 0.06$). The authors noted that the small number of subjects limited the statistical power of the study.

Zavalic et al. (1998) examined the effects of chronic occupational toluene exposure on color vision using a group of 45 exposed workers (mean toluene exposure concentration = 120 ppm) and 53 controls. Color vision was evaluated using the Lanthony desaturated panel D-15 test; test scores were age and alcohol consumption-adjusted. Color vision was significantly impaired in toluene-exposed workers ($p < 0.0001$) compared to controls. It was also observed that there was no significant difference between test scores on Monday morning (prework) and Wednesday morning. The authors stated that the effect of toluene on color vision can be chronic and that the possible recovery period is longer than 64 hours.

**Hepatic Effects**

Greenburg et al. (1942) reported liver enlargement in 32 of 106 (30.2%) painters employed in an aircraft factory compared to 7% in a control group. However, there was some exposure to other solvents (ethanol, ethyl acetate, butyl acetate) and paint ingredients such as zinc chromate.

Liver toxicity has been reported in toluene solvent abusers (Fornazzari et al., 1983). Eight of 24 solvent abusers demonstrated abnormal results in three liver function tests; however, the tests used were not specified. The test parameters returned to normal after two weeks of toluene abstinence, suggesting that any liver damage caused by toluene abuse in those patients was not long lasting.

A cross-sectional study by Boewer et al. (1988) showed no significant correlation between toluene exposure and the levels of serum enzymes (serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyltransferase (GGT)) considered to be indicators of hepatic damage. In another cross-sectional study of 289 printing workers exposed to less than 200 ppm for 8 hours/day, 8 workers had significantly elevated serum enzymes (ALT/AST ratio, mean = 1.61) potentially indicative of liver damage. In each case, liver biopsy indicated a mild pericentral fatty change (Guzelian et al., 1988). However, the mean toluene exposure concentration was not reported (only an upper bound), and no control group was included in the study.

V. Effects of Animal Exposures

**Neurotoxic Effects**

Sprague-Dawley rats (15/sex/group) were exposed to 0, 100, or 1481 ppm toluene for 6 hours/day, 5 days/week for 26 weeks (API, 1981). Neurohistopathological examinations were conducted in 3-5 rats/sex/group at weeks 9, 18, and 27. No significant treatment-related effects were reported. The study usefulness was limited because there were no other neurohistopathological examinations or organ weight measurements conducted on the animals.

Forkman et al. (1991) studied the potential neurotoxicity of toluene inhalation exposure (3700 mg/m$^3$ (1000 ppm), 21 hours/day, 5 days/week for 4 weeks) in male Sprague-Dawley rats. The rats were either trained in behavior meant to be performance tested and then exposed to toluene, or exposed and then trained. The rats were then subjected to several behavioral tests, including an operant test with baseline performance and extinction, motor coordination, and exploratory activity. All tests were performed from 11 to 35 days after the end of the exposure. Exposure of trained rats to toluene resulted in a significantly different overall test
performance when compared to controls. Rats trained after toluene exposure also had test performances different from controls, but the difference was not statistically significant.

Rats exposed to toluene concentrations of 1000 ppm or 100 ppm, 6 h/day, 5 days/week, for 3 or 6 months, respectively, demonstrated statistically significant decreased motor function as measured by degraded performance (approximately 60% and 65% of control at 1000 and 100 ppm toluene, respectively) on a rotarod performance test and decreases in spontaneous motor activity (approximately 62% of control at 100 ppm toluene) (Korsak et al., 1992).

von Euler et al. (1993) studied the effects of subchronic toluene inhalation exposure (80 ppm, 4 weeks, 5 days/week, 6 hours/day) on spatial learning and memory, dopamine-mediated locomotor activity and dopamine D2 agonist binding in rats. Spatial learning (postexposure days 3-6) and memory (postexposure day 14) were tested using a water maze. Spontaneous and apomorphine-induced locomotor activity was evaluated on postexposure day 17. Effects on binding parameters of the dopamine D2 agonist S(-)[N-propyl-3H(N)]-propynorapomorphine ([H]NPA) were determined using membrane preparations of the neostriatum of the rat brain. Toluene exposure caused a statistically significant impairment in spatial learning and memory. Toluene also significantly increased apomorphine-induced locomotion and motility but not rearing. Spontaneous locomotion, motility and rearing were not affected by toluene. Toluene exposure significantly increased the $B_{max}$ and $K_D$ values for $[^3H]$NPA binding. These results indicate that subchronic toluene exposure of rats to toluene causes persistent deficits in spatial learning and memory, a persistent increase in dopamine-mediated locomotor activity and an increase in the number of dopamine D2 receptors in the neostriatum.

Male rat exposure to toluene (0, 40, 80, 160 or 320 ppm, 4 weeks, 6 hours/day, 5 days/week), followed by a postexposure period of 29–40 days, resulted in decreased brain wet weights of the caudate-putamen (trend test for dose-response significant at $p < 0.05$) and subcortical limbic areas (trend test for dose-response significant at $p < 0.01$; significantly less than controls ($p < 0.001$) at concentrations of 80 ppm and higher) (Hillefors-Berglund et al., 1995). Toluene exposure also significantly altered dopamine receptor activity (trend test for dose-response) as indicated by decreased $IC_{50}$ (inhibition constant) (significantly less than controls ($p < 0.05$) at 80 ppm), $K_H$ (inhibition constant for high-affinity receptor sites), $K_L$ (inhibition constant for low-affinity receptor sites), and $R_H\%$ (high-affinity receptor site specific binding) values for dopamine competitive inhibition of $[^3H]$raclopride-binding in the caudate-putamen. Toluene exposure did not significantly affect the wet weights of the whole brain, serum prolactin levels, the $K_D$ (disassociation constant) or the $B_{max}$ (maximal specific binding) values of $[^3H]$raclopride-binding in the caudate-putamen and the subcortical limbic area, or the effect of dopamine on $IC_{50}$ values at $[^3H]$raclopride-binding sites in the subcortical limbic area. Exposure to xylene or styrene (80 and 40 ppm, respectively; 4 weeks, 6 h/day, 5 days/week) followed by a postexposure period of 26-32 days had no effect on the parameters described above. The authors concluded that long-term exposure to low concentrations of toluene ($\geq 80$ ppm), but not xylene (80 ppm) or styrene (40 ppm), leads to persistent increases in the affinity of dopamine D2 agonist binding in the rat caudate-putamen. The authors also suggested that the enhancement of apomorphine-induced locomotor activity seen after toluene exposure by von Euler et al. (1993) may be related to the increased D2 agonist activity described above ($IC_{50}$, $K_H$, $K_L$ values).

Respiratory Effects

A study of the chronic effects of toluene in rats (5-20 animals per group) exposed for 106 weeks to 0, 30, 100, or 300 ppm (0, 113, 375, or 1125 mg/m$^3$) toluene showed no treatment-related effects on histopathology of major organs, including the nasal turbinates (CIIT, 1980). In this study, the nasal histopathology examination sampling may have been inadequate to demonstrate the nasal lesions reported by the NTP (1990).

Rats (20 per group) exposed for 2 years to 0, 600, or 1200 ppm (0, 2261, or 4523 mg/m$^3$) toluene 6.5 hours/day, 5 days/week for 103 weeks were examined for hematological and histopathological effects in addition to gross observations of toxicity (NTP, 1990). Significant erosion of the olfactory epithelium was
observed in male rats while degeneration of the respiratory and nasal epithelium was observed in both sexes at 600 ppm.

Mice were exposed chronically to 0, 120, 600, or 1200 ppm (0, 452, 2261, or 4523 mg/m$^3$) toluene 6.5 hours/day, 5 days/week, for 2 years (NTP, 1990). The only treatment-related effect was a significant increase in the number of animals with hyperplasia of the bronchial epithelium in the 1200 ppm exposure group.

**Reproductive and Developmental Toxicity**

Reproductive toxicity to maternal rats was observed during exposure to 1500 ppm toluene, 24 hours/day on days 9 to 14 of gestation (Hudak and Ungvary, 1978). Two dams out of 19 died during exposure. Fetuses from the 1500 ppm group showed increased incidence of sternebral alterations, extra ribs and missing tails. The same exposure on days 1 through 8 of gestation resulted in 5 deaths out of 14 dams. Fetuses in this regimen showed increased incidence of hydrocephaly and growth retardation compared to controls. A third regimen that exposed maternal rats to 1000 ppm on days 1 through 21 of gestation resulted in no maternal deaths or toxicity, and an increase in the incidence of skeletal variations in the fetuses. When exposed to 1500 ppm continuously, maternal mice died within 24 hours of exposure whereas exposure to 500 ppm had no apparent effect. Examination of the fetal mice showed significant growth retardation in the 500 ppm group.

A 2-generation study of the effects of 0, 100, 500, or 2000 ppm (0, 377, 1885, or 7538 mg/m$^3$) toluene in rats (males, 10-40 per group; females, 20-80 per group) was done by the American Petroleum Institute (API)(1985). Rats were exposed for 6 hours/day, 7 days/week for 80 days and a 15 day mating period. The mated females were then exposed to the same concentrations during days 1-20 of gestation and days 5-20 of lactation. After weaning, the F$_1$ pups were exposed 80 times to the appropriate exposure level and then randomly mated to members of the same exposure group. The F$_1$ generation showed significantly decreased body weight which persisted throughout lactation. No effects were observed on histopathology. No data were presented for the F$_2$ generation.

Da Silva et al. (1990) exposed rats and hamsters to 0 or 800 mg/m$^3$ toluene for 6 hours/day on gestation days 14-20 (rats), or days 6-11 (hamsters). Exposed rats demonstrated a significant exposure-related decrease in birth weight compared with controls. In addition to low birth weight, the number of live pups was significantly lower in the 800 ppm group. No deficits in any parameter were noted in the hamsters. In this study, no neurobehavioral effects were noted in the offspring.

Hass et al. (1999) exposed rats to 0 or 1200 ppm toluene for 6 h per day from day 7 of pregnancy until day 18 postnatally. Developmental and neurobehavioral effects in the offspring were investigated using a test battery including assessment of functions similar to those in the proposed Organization for Economic Cooperation and Development (OECD) Testing Guidelines for Developmental Neurotoxicity Study (physical development, reflex development, motor function, motor activity, sensory function, and learning and memory). The exposure did not cause maternal toxicity or decreased offspring viability. However, lower birth weight, delayed development of reflexes, and increased motor activity in the open field was noted in the exposed offspring. The exposed female offspring had poorer scores on a Morris water maze test (they took longer to locate a hidden platform after platform relocation) at the age of 3.5 months indicating impaired cognitive function. The difference was not related to impaired swimming capabilities since swim speeds were similar to control values. The authors stated that exposure to 1200 ppm toluene during brain development caused long-lasting developmental neurotoxicity in rats.

Toluene has been listed under Proposition 65 as being known to the State of California to cause reproductive toxicity (OEHHA, 1999). Its NSRL is 7,000 micrograms per day.
### VI. Derivation of Chronic Reference Exposure Level (REL)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hillefors-Berglund <em>et al.</em> (1995); supported by Orbaek and Nise (1989), Foo <em>et al.</em> (1990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>Male Sprague-Dawley rats</td>
</tr>
<tr>
<td>Exposure method</td>
<td>Inhalation</td>
</tr>
<tr>
<td>Critical effects</td>
<td>Decreased brain (subcortical limbic area) weight, Altered dopamine receptor (caudate-putamen) binding</td>
</tr>
<tr>
<td>LOAEL</td>
<td>80 ppm</td>
</tr>
<tr>
<td>NOAEL</td>
<td>40 ppm</td>
</tr>
<tr>
<td>Exposure continuity</td>
<td>6 hours/day, 5 days/week</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>4 weeks, followed by 29-40 days recovery</td>
</tr>
<tr>
<td>Average experimental exposure</td>
<td>7 ppm (40 × 6/24 hours × 5/7 days)</td>
</tr>
<tr>
<td>Human equivalent concentration</td>
<td>7 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that $\lambda_a = \lambda_h$)</td>
</tr>
<tr>
<td>Subchronic uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Interspecies uncertainty factor</td>
<td>1 (see below)</td>
</tr>
<tr>
<td>Intraspecies uncertainty factor</td>
<td>10</td>
</tr>
<tr>
<td>Cumulative uncertainty factor</td>
<td>100</td>
</tr>
<tr>
<td>Inhalation reference exposure level</td>
<td>0.07 ppm (70 ppb; 0.3 mg/m$^3$; 300 µg/m$^3$)</td>
</tr>
</tbody>
</table>

| Supportive human study | Foo *et al.* , 1990 |
| Study population | 30 female workers in an electronic assembly plant |
| Exposure method | Occupational inhalation |
| Critical effects | Neurobehavioral deficits in 6 out of 8 tests |
| LOAEL | 88 ppm |
| NOAEL | Not observed |
| Exposure continuity | 10 m$^3$/day occupational inhalation rate, 5 days/week |
| Average occupational exposure | 31.4 ppm (88 ppm x 10/20 x 5/7) |
| Exposure duration | 5.7 ± 3.2 years (exposed group); 2.5 ± 2.7 years (controls) |
| LOAEL uncertainty factor | 10 |
| Subchronic uncertainty factor | 3 |
| Interspecies uncertainty factor | 1 |
| Intraspecies uncertainty factor | 10 |
| Cumulative uncertainty factor | 300 |
| Inhalation reference exposure level | 0.1 ppm (100 ppb; 0.4 mg/m$^3$; 400 µg/m$^3$) |

The critical animal study (Hillefors-Berglund *et al.*, 1995) used to derive an REL for toluene describes adverse neurological effects in rats after a well characterized inhalation exposure to toluene. The study results contain both a LOAEL and a NOAEL. Decreased brain (subcortical limbic area) weight and altered dopamine receptor binding compared to controls were noted at the NOAEL, but the changes were not statistically significant; this suggests that if a threshold for adverse neurological effects exists in this study, it would be at or below the observed NOAEL. The study LOAEL for altered dopamine receptor binding agrees qualitatively with results from similar studies (von Euler *et al.*, 1994). Additionally, toluene-induced neurotoxicity has been described in many studies by a variety of endpoints in both animals and humans (ATSDR, 1999). The adverse neurotoxic effects associated with toluene exposure in the rat study by Hillefors-Berglund *et al.* (1995), decreased brain (subcortical limbic area) weight and altered dopamine receptor binding, occur in areas of the rat brain that are structurally and functionally similar to 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). Table 1 lists several Reference Exposure Levels (RELS)
calculated from the most sensitive animal and human neurotoxicity studies available. These RELs are also protective for other adverse endpoints, such as respiratory tract damage and teratogenicity.

Table 1: Reference Exposure Levels (RELs) from Selected Neurotoxicity Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Effect</th>
<th>LOAEL (ppm)</th>
<th>LOAEL (ppm) (TWA)</th>
<th>NOAEL (ppm)</th>
<th>NOAEL (ppm) (TWA)</th>
<th>total UF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>REL (ppb)</th>
<th>REL (µg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VonEuler et al. (1988)</td>
<td>4 weeks</td>
<td>rat: altered brain dopamine receptor binding</td>
<td>80</td>
<td>14.3</td>
<td>1000</td>
<td>14</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbaek and Nise&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29 years</td>
<td>human: impairment on neuropsychometric tests</td>
<td>11.2 - 41</td>
<td>4 - 14.6</td>
<td>100</td>
<td>40 - 146</td>
<td>150 - 551</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foo (1990)</td>
<td>5.7 years</td>
<td>human: neurobehavioral tests</td>
<td>88</td>
<td>31.4</td>
<td>300</td>
<td>105</td>
<td>394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korsak (1992)</td>
<td>6 months</td>
<td>rat: impaired motor function</td>
<td>100</td>
<td>17.9</td>
<td>100</td>
<td>179</td>
<td>671</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hillefors-Berglund et al. (1995)</td>
<td>4 weeks</td>
<td>rat: decreased brain (subcortical limbic area) weight; altered brain dopamine receptor binding</td>
<td>80</td>
<td>14.3</td>
<td>40</td>
<td>7.1</td>
<td>100</td>
<td>71</td>
<td>271</td>
</tr>
</tbody>
</table>

LOAEL: Lowest Observable Effect Level; NOAEL: No Observable Effect Level
REL: Reference Exposure Levels; TWA: time-weighted average

a: Uncertainty Factors used to derive RELs
- VonEuler et al. (1988): LOAEL to NOAEL UF = 10, subchronic to chronic UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 1000.
- Orbaek and Nise (1989): LOAEL to NOAEL UF = 10, intraspecies variability = 10; total UF = 100
- Foo et al. (1990): LOAEL to NOAEL UF = 10, subchronic to chronic UF = 3, intraspecies variability = 10; total UF = 300
- Korsak et al. (1992): LOAEL to NOAEL UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 100.
- Hillefors-Berglund et al. (1995): Subchronic to chronic UF = 10, animal to human UF = 1, intraspecies variability = 10; total UF = 100.

b: Pooled psychometric data from two printing plants with different toluene concentrations (11.2 and 41 ppm) were used to determine significant neurotoxic effects by Orbaek and Nise (1989). The range of RELs derived from that study lists the upper and lower bounds for risk associated with the pooled population exposures. ATSDR (1999) used the Orbaek and Nise (1989) study data, assuming an exposure concentration of 11.2 ppm, to derive a chronic inhalation minimal risk level (MRL).

If both human and animal adverse effect data on a chemical are available, OEHHA prefers to use the human data to develop a REL when possible. However, the study by Hillefors-Berglund et al. (1995) provides data (decreased brain [subcortical limbic area] weight and altered brain dopamine receptor binding) which are specific and sensitive measures of neurotoxicity that would not be obtainable in human studies. In contrast, the psychometric tests used to generate the neurotoxicity data in the human occupational exposure studies described above tend to be less sensitive and suffer from greater measurement uncertainty. Additionally, the Hillefors-Berglund et al. (1995) study has better exposure characterization than the human occupational exposure studies. Nonetheless, the human studies are useful in supporting the derivation of the REL for toluene. Ordinarily, an interspecies uncertainty factor of 3 would be applied, in addition to the human equivalent concentration calculation, to reflect the uncertainty associated with extrapolating from animals to humans. However, in this case the uncertainty in the interspecies extrapolation is reduced by the availability of human epidemiological data with generally consistent effect levels, after appropriate duration corrections. Based on comparison of the data in both animals and humans, it appears that a REL of 271 µg/m<sup>3</sup> (rounded to 300 µg/m<sup>3</sup> in the final derivation) would protect exposed humans from experiencing chronic neurotoxic effects.
VII. Data Strengths and Limitations for Development of the REL

The major strength of the REL for toluene is the use of an animal study with accurate exposure characterization and both LOAEL and NOAEL observations for an effect (neurotoxicity), supported by observations from other animal and human studies. A weakness is the uncertainty in predicting human health risk from animal adverse effect data. However, this is mitigated by the availability of human data showing effect levels that are, after appropriate corrections, broadly consistent with the animal data.

VII. References


