Public Health Goal for Toluene In Drinking Water

Prepared by

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without

regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR TOLUENE IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has developed a Public Health Goal of 0.15 mg/L (150 ppb) for toluene in drinking water. This is based on a subchronic study in which toluene was administered to mice via drinking water. Significantly increased liver weights (hepatomegaly) and decreased thymus weights were observed at a treatment level of 105 mg/kg per day but not at 22 mg/kg per day. From this study, a NOAEL of 22 mg/kg-day was identified. Because of the volatility of toluene, we assumed a relative source contribution of 40% and adult drinking water consumption levels of 4 liters/day. A factor of 1,000 (10-fold for inter-species variation, 10-fold for human variability, 10-fold to account for the use of a subchronic study for determining a lifetime value) was used to account for uncertainty in the PHG calculation. The current U.S. Environmental Protection Agency (U.S. EPA) Maximum Contaminant Level (MCL) for toluene in drinking water is 1 mg/L (1 ppm).

INTRODUCTION

The purpose of this document is to develop a PHG for toluene. Toluene is a volatile, reactive aromatic hydrocarbon that is nearly insoluble in water. It is fairly rapidly degraded and generally does not persist in the environment. Toluene is principally used in gasoline blending, but also as a solvent for paints, adhesives and many other products. Generally, human exposure to toluene is via the inhalation route, either occupationally or by intentionally inhaling the vapors as a drug of abuse. Significant exposures of toluene to humans are usually occupational, such as rotogravure printing operations, or by intentional inhalation as a drug of abuse. Toluene is not commonly found in drinking water in California.

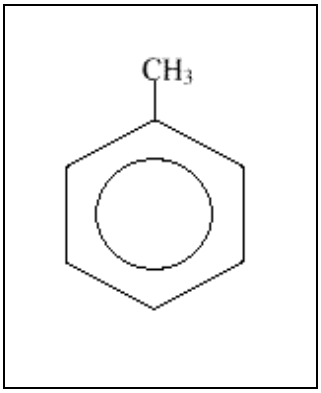
CHEMICAL PROFILE

Chemical Identity

Table 1. Chemical Identity of Toluene

Chemical Name	Toluene
Synonyms	Methylbenzene, phenylmethane
Registered trade name	Metacide, methylbenzol, toluol
Chemical formula	$C_6H_5CH_3$
Wiswesser line notation	IR
CASRN	108-88-3

Chemical structure



Physical and Chemical Properties

Physical and chemical properties of Toluene are given in Table 2. Toluene is only slightly soluble in water and is miscible with organic solvents.

Table 2. Physical and Chemical Properties of Toluene

Property	**Value or Information**	**References**
Molecular weight	92.1	NIOSH, 1994
Color	colorless	NIOSH, 1994
Physical state	liquid	NIOSH, 1994
Odor	sweet, pungent, benzene-like	NIOSH, 1994
Odor threshold	0.04 mg/L (in water)	U.S. EPA, 1995
Melting point	-95^0C	U.S. EPA, 1995
Boiling point	111^0C	U.S. EPA, 1995
Flash point	40^0F	NIOSH, 1994
Flammability limits	UEL:7.1%, LEL:1.1%	NIOSH, 1994
Autoignition temperature	480 ^{0}C	HSDB, 1996
Solubility		
Water	0.07 % @ 24^0 C, slightly sol.	NIOSH, 1994; U.S. EPA, 1995
Water	535 mg/L @ 25^0 C	U.S. EPA, 1991; ATSDR, 1994
Organic solvents	Miscible with alcohol, acetone, benzene, ethyl ether, others	HSDB, 1996
Specific gravity, density	0.866 @ 20^0C	U.S. EPA, 1995
Partition coefficients		

Property	Value or Information	References
Log K_{ow}	2.69	U.S. EPA, 1995
Soil sorption coefficient K_{oc}	range: 37-178, moderate to very high mobility in soil	U.S. EPA, 1995
Bioconcentration factor	<100, fish; <10, shellfish, not expected to bioconcentrate	U.S. EPA, 1995
Vapor pressure	36.7 mmHg@30^0C	U.S. EPA, 1995
Conversion factor	1 ppm = 3.83 mg/m^3	NIOSH, 1994

Production and Uses

The production of toluene in the U.S. in 1984 totaled 725.8 million gallons (5.25 billion pounds). In 1993, this increased to 6.4 billion pounds. Of this, an estimated 83% of the toluene remains unisolated for use in gasoline. Approximately 50% of the isolated toluene (17% of the total production) is back-blended into gasoline to increase octane ratings, 33% is used in the production of benzene, and 7% is used as a solvent in paints, coatings, adhesives, pharmaceuticals, inks, and related products. The remainder is used in the production of toluene diisocyanate and other chemicals (U.S. EPA, 1990; U.S. EPA, 1995; HSDB, 1996).

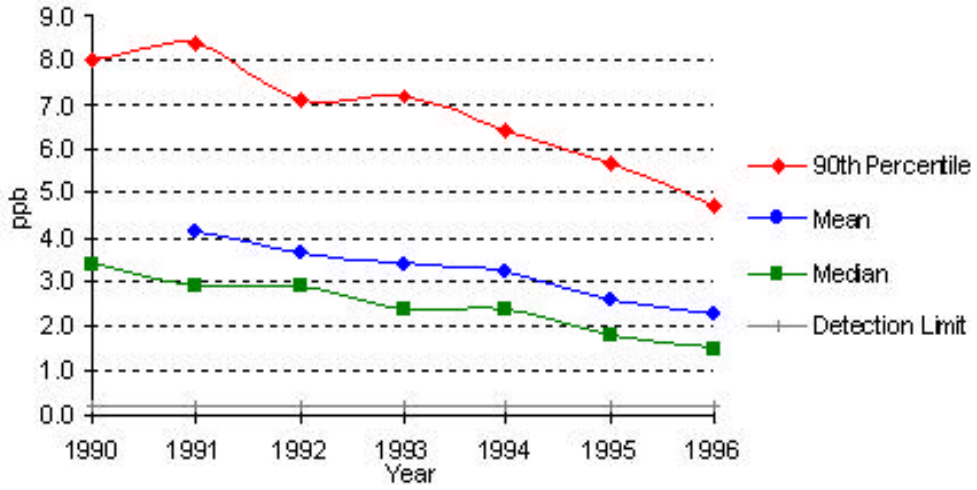
ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Most of the toluene entering the environment is released directly to the atmosphere. The largest combined source is production, transport, and use of gasoline, which is 5-7% toluene by weight (ATSDR, 1994). Toluene is also used in paints, solvents, adhesives, inks, and similar products, and escapes to the atmosphere upon use (ATSDR, 1994). Automobile emissions are also a principle source of toluene to the ambient air (ATSDR, 1994).

For California in 1996, the mean statewide concentration for airborne toluene was measured as 2.26 ppb (CARB, 1998). As the following graph indicates, the statewide mean ambient concentrations of toluene have dropped steadily since 1991.

Figure 1, 1990 - 1996 Statewide Summary of Airborne Toluene, ppb



source: California Air Resources Board, 1998

Atmospheric toluene is degraded by reaction with photochemically produced hydroxyl radicals with the half-life of toluene in the atmosphere ranging from three hours to slightly greater than one day. It is not subject to direct photolysis. Toluene can also be washed out of the atmosphere by rain (U.S. EPA, 1995).

Soil

According to the World Health Organization (WHO, 1985) toluene probably exists adsorbed onto soils, with the adsorption capacity varying inversely with the pH of the soil. The authors speculate that a portion of the toluene in soil will transfer to air and water media, and that the part that remains in soil may participate in chemical reaction, biological degradation, and transformation (WHO, 1985). U.S. EPA (1995) reports that toluene released to the soil will be lost by evaporation from the near-surface soil and by leaching to the groundwater. The breakdown of toluene by soil microbes is slow. Releases to land and soil can occur from such sources as gasoline spills, leaking underground storage tanks, and land disposal of municipal sludge and refinery wastes (ATSDR, 1994).

Water

As toluene is a volatile aromatic chemical with low water solubility, it is expected to evaporate from water into the ambient air. The physical properties of toluene are such that it highly favors the vapor state (U.S. EPA, 1990). Long-term monitoring has consistently shown that toluene is rarely found in drinking water sources in the state of California (DHS, 1998). The most recent data, from 1984 through the end of 1996, are given in Table 3.

Table 3. Toluene Measured in California Drinking Water, 1984-1996

Number of samples for toluene .....…….....	13,349
Number of locations toluene detected .....….....…	19
Number of locations measured toluene exceeded Federal MCL*	1

*(MCL = 1 ppm)

These data from (DHS, 1998) are somewhat limited for practical use. For example, there is no information on the relationship of the presence of toluene detected in well water to the concentration of toluene in tap water. Further, there is no information on the specific populations potentially served by individual contaminated wells.

Food

Little information exists in the scientific literature regarding the bioaccumulation of toluene in food. With the exception of fish and seafood exposed to toluene through proximity to accidental spills or industrial discharge, little information is available on amounts of toluene potentially present in human food sources (U.S. EPA, 1980; WHO, 1985; U.S. EPA, 1990).

METABOLISM AND PHARMACOKINETICS

Absorption

Data from human and animal studies were used to estimate pulmonary absorption efficiency for toluene. In a review of eight human studies, the range of uptake efficiency was estimated to be 49 to 83% with a mean of 58% (Carlsson and Lindqvist, 1977; Nomiyama and Nomiyama, 1978; Carlsson, 1982; Benoit et al., 1985; Wallen et al., 1985; Wallen, 1986; Brugnone et al., 1986; Ovrum et al., 1978). The uptake of toluene by the lungs of experimental animals ranged from 26 to 93% with a mean of 60% (Egle, 1976; Hobara et al., 1884; Bergman, 1979).

Gospe and Al-Bayati (1994) compared oral and inhalation exposures to toluene in the rat. Male Fisher-334 rats were exposed to ^{14}C-toluene by gavage or inhalation. Oral doses of 110, 336, 741, and 911 mg toluene/kg body weight were administered to 82 rats and blood toluene levels were followed for six hours. For the 120 rats in the inhalation group, three-hour exposures were given at 10, 99, 549, or 1,145 ppm. Blood toluene levels measured during the uptake (exposure) phase and for a four-hour elimination period. The data from the two exposure methods were fitted to parametric kinetic models, and the resulting curves integrated. The authors concluded that the oral dosing produces blood toluene levels that are similar to those produced by inhalation;

however the shape of the time-concentration profile differs for the two methods. Inhalation curves of concentration versus time reached asymptotic levels by one to two hours, however, oral blood toluene-time curves reached asymptotic levels from 1.6 to 6.3 hours post exposure. This suggests a slower absorption via the oral route as the concentration increased (Gospe and Al-Bayati, 1994).

In animals, dermal absorption of toluene appeared to reach a steady-state concentration approximately two to three hours following application (Jakobson et al., 1982; Tsuruta, 1982). Absorption of toluene by male mouse skin (30-40 g-b.w.) was estimated to occur at a rate of 34.4 ± 9.1 $\mu g/cm^2$ (Tsuruta, 1996). In humans, the dermal absorption rates of undiluted toluene and toluene in an aqueous solution were reported to range from 14 to 23 mg/cm^2-hour and 0.16 to 0.6 mg/cm^2-hour, respectively, dependent on concentration (Dutkiewicz and Tyras, 1968).

Distribution

Toluene is an aromatic hydrocarbon with a high affinity for lipid-rich tissue, including those in the central nervous system (Arnold et al., 1994). In the rat, maximum tissue levels of toluene were achieved at two to three hours after oral administration of 4-[^{3}H]-toluene dissolved in peanut oil (Pyykko et al., 1977). Absorbed toluene distributes initially to the lipid-rich tissues such as the brain, kidney, and the liver and ultimately accumulates principally within the adipose tissues (Sato, 1988; Environment Canada, 1992). Toluene was detected in the following tissues in order of decreasing percentage: adipose tissue (white and brown), stomach, liver, kidneys, bone marrow, brain and spleen. Peak radioactivity in white adipose tissue (approximately 250 times the concurrent blood concentration) was reached at five hours. Compared to oral administration, toluene was more rapidly distributed following inhalation (15 to 30 minutes), with similar patterns of tissue distribution (Pyykko et al., 1977; Bruckner and Peterson, 1981; Bergman, 1983; Gospe and Al-Bayati, 1994). In rats, white adipose tissue retained the highest concentration of radioactivity (Carlsson and Lindqvist, 1977).

In human volunteers exposed to 80 ppm (306 mg/m^3) toluene for four, 30-minute periods at rest or in conjunction with exercise, the respective concentrations of toluene in subcutaneous fat were 0.7 and 9.9 mg/kg (Carlsson and Ljungquist, 1982). Carlsson and Ljungqvist (1982) also investigated the effect of body fat on the distribution of toluene in exposed men. The estimated percentage of total toluene uptake retained in adipose tissue one hour post-exposure was 4.6% in the leanest man and 20% in the most obese. Three days after exposure, the respective fractions were estimated as 0 and 12.4%. Exercise increased the ratio of the concentration of toluene in subcutaneous fat to the concentration in arterial blood.

Metabolism

Toluene is metabolized via sequential hydroxylation and oxidation to benzoic acid. The conjugation of glycine with benzoic acid to form hippuric acid constitutes the major route of toluene detoxification and elimination. In addition to conjugation with glycine, small amounts of benzoic acid may be conjugated with glucuronic acid and excreted as benzoyl glucuronide (U.S. EPA, 1990; Wilkins-Haug, 1997). Less than 1% of the toluene administered via various routes may undergo hydroxylation to form *o*- or *p*-cresol which are conjugated to glucuronide or sulfate and excreted in urine (Bakke and Scheline, 1970; Woiwode and Drysch, 1981; Angerer and Kraemer, 1996; Wilkins-Haug, 1997).

Cytochrome P-450-dependent enzymes in the liver predominantly metabolize toluene. Induction of hepatic microsomal cytochrome P-450 levels by phenobarbital increased the rate of metabolism of toluene and the excretion of hippuric acid in rats (Ikeda and Ohtsuji 1971). Several investigators have reported induction of cytochrome P-450-dependent enzymic activities by toluene (Toftgard et al., 1982; Pathiratne et al., 1986). Hepatic glutathione, glutathione-*S*-transferase, 7-ethoxycoumarin-*O*-deethylase, and 7-ethoxyresorufin-*O*-deethylase levels were also reportedly increased by toluene exposure to animals (van Doorn R et al., 1980; Chand and Clausen, 1982; Pyykko K et al., 1987). Conversely, the level of cytochrome P-450 activity in lung tissue was significantly lower in toluene-treated rats compared to the untreated rats.

Excretion

Toluene is excreted primarily through the lungs as the parent compound or in the urine as metabolites. The relative excretory rates for these different pathways are species-specific. For example, in mice and rats approximately 10 and 40% of the administered toluene was eliminated respectively in expired air, and 68 and 60%, was eliminated respectively in urine as hippuric acid and other metabolites (Nomiyama and Nomiyama, 1978; Bergman, 1979; Ogata and Fujii, 1979). In human volunteers, 4 to 21% of the total inhaled toluene was reported to be eliminated by the lungs and 60 to 80% in the urine as hippuric acid and other metabolites including benzoyl glucuronide (Veulemans and Masschelein, 1978; Veulemans and Masschelein, 1979; Nomiyama and Nomiyama, 1978; Riihimaki, 1986; U.S. EPA, 1990).

There are several studies of toluene elimination in humans. A positive correlation between the concentration of toluene in alveolar air and in blood both during and after exposure has been demonstrated (Sato et al., 1974; Carlsson, 1982; Brugnone et al., 1986). Nomiyama and Nomiyama (1978) reported that the excretion of hippuric acid in humans exposed to 107 ppm toluene in air reached a maximum rate of approximately 190 mg/hour within two hours of the start of exposure. These investigators also estimated elimination half-life for toluene-derived hippuric acid to be 117 and 74 minutes in males and females, respectively (Nomiyama and Nomiyama, 1978).

For humans, the elimination of hippuric acid is not considered as reliably associated with toluene exposure as it was formerly considered to be. The variation among individuals within the human population is too large for this association to be considered suitable for biological monitoring. One possible explanation for the variability is the differing levels of benzoic acid within the human diet (Nise, 1992; Lof et al., 1993).

TOXICOLOGY

Toxicological Effects in Animals and Plants

Toxic effects to the central nervous system (CNS), cardiovascular, hematopoietic, reproductive, and respiratory systems, as well as to the liver, kidneys, skin, and sensory organs have been reported for toluene. Prior to the mid-1950s benzene was often a contaminant of toluene, with concentrations as high as 20%. Consequently, some adverse effects observed in animals may not be attributed solely to toluene, especially in studies performed before 1960 (Fishbein, 1988; U.S. EPA, 1990).

Acute Toxicity

The acute toxicity of toluene either inhaled or ingested, is relatively low (Environment Canada, 1992). Estimates for median lethal doses (LD_{50}, LC_{50}) for acute toluene exposures have been reviewed (NTP, 1990; U.S. EPA, 1990; OEHHA, 1992; ATSDR, 1994). The median lethal dose of toluene was estimated in rats, mice, guinea pigs, and rabbits for various routes of exposure (Reed et al., 1989). In rats, the oral LD_{50}s range from 2,600 to 7,530 mg/kg. Lethal doses following dermal administration are 1.5 to 5-fold higher than those for ingestion. The range of LC_{50} values for inhalation is 20,299 to 153,200 mg/m^3 (5300 to 40,000 ppm) depending on the duration of exposure and the species (OEHHA, 1992).

Narcosis, instability, incoordination, depression, restlessness, tremors, and prostration were consistently observed in rats and mice exposed to high doses of toluene via inhalation (Bruckner and Peterson, 1981; Molnar et al., 1986). Various related manifestations have occurred over a wide range of exposures, including limb paralysis and contractions, headshakes, and loss of the righting reflex (Hinman, 1984; Kjellstrand et al., 1985; Molnar et al., 1986; Hinman, 1987).

In addition to CNS effects, adverse effects were also reported in the liver and cardiovascular systems. Increases in relative liver weight and cytochrome P-450 levels were reported in rats, mice and rabbits and increases in cytochrome b_5 concentration were observed in rats and rabbits (Elovaara et al., 1979; Chand and Clausen, 1982; Pyykko, 1983; Hsieh et al., 1989; NTP, 1990).

Analyses of the electrocardiograms of rats receiving short-term exposure to toluene revealed irregularities including bradyarrhythmias, asystoles, slowing of the sinoatrial rate, prolongation of QRS and PR intervals, tachycardia, and decreased intraventricular and atrioventricular conduction (Taylor and Harris, 1970; Morvai et al., 1976; Vidrio et al., 1986). Cardiac sensitization to asphyxia-induced atrioventricular block was also observed in rats (Taylor and Harris, 1970).

Subchronic Toxicity

Wolf et al. (1956) conducted a subchronic oral toxicity study of toluene in female Wistar rats. Ten rats were intubated with toluene in olive oil at 118, 354, or 590 mg/kg, five days per week, for a total of 138 exposures over 193 days. Twenty control rats were intubated with an equivalent volume of vehicle. Toxicity was evaluated by behavioral, hematological, and gross examinations. In addition, liver, lung, heart, spleen, pancreas, bone marrow, and kidney tissues were examined histologically. No signs of toxicity were observed at any treatment level; therefore, an oral NOAEL of 590 mg/kg-day can be derived from this study. The average daily dose at this level, adjusting for the five day per week dosing schedule, was calculated to be 421 mg/kg-day (Wolf et al., 1956).

The National Toxicology Program (NTP) sponsored 13-week oral studies in rats and mice (NTP, 1990). Only the rat study is presented here as the rat was the more sensitive species in this assay. Groups of 10 Fischer-344 rats (six to seven weeks old) of each sex were intubated with 10 mL/kg toluene in corn oil at concentrations of 31.2, 62.5, 125, 250, or 500 mg/mL, corresponding to respective doses of 312, 625, 1,250, 2,500 or 5,000 mg/kg-day, for five days per week for 13 weeks. Identical groups of animals intubated with only the vehicle served as the controls. Comprehensive hematological and urine analyses were conducted on all animals surviving to the end of the study. All animals were examined for gross lesions.

Increases of liver and kidney weights in male rats were observed at 625 mg/kg-day and at higher doses (NTP, 1990). Changes in the tubules of the cortical area of the kidney were observed in one male rat in the 1,250 mg/kg group and in a majority of the rats in the 2,500 and 5,000 mg/kg groups that died prior to terminal sacrifice. These changes included swollen tubules, degeneration and necrosis of tubular epithelia, and the presence of casts in the tubular lumina. Rats killed at the end of the study exhibited regeneration and cystic dilation of the tubules, suggesting the initiating of compensatory repair. Histological observation of the brains of rats in the 1,250 and 2,500 mg/kg dose groups revealed scattered mineralized foci and/or necrosis of neuronal cells. At 2,500 and 5,000 mg/kg, additional toxic effects were observed; these included hypoactivity, prostration, ataxia, piloerection, lacrimation, excessive salivation, decreased body weight, urinary bladder hemorrhage, congestion and lesions in major organs, and death. From these results OEHHA derived a NOAEL of 312 mg/kg-day (U.S. EPA, 1990; IRIS, 1997). The average daily dose at this level, considering a dosing schedule of five days per week, was calculated to be 223 mg/kg-day.

NTP also sponsored two toluene inhalation studies in rats and mice (NTP, 1990). Groups consisting of 10 male and 10 female B6C3F1 mice (eight weeks old) were exposed to 94, 611, 1,104, 2,311, or 2,931 ppm toluene (purity 100%) in air, six hours per day, five days per week for 14 weeks. Groups consisting of 10 male and 10 female Fischer-344 rats (six to seven weeks old) were exposed to 93, 601, 1,084, 2,301, or 2,926 ppm toluene in air, six hours per day, five days per week for 15 weeks. Identical groups of animals exposed to filtered air served as controls. Toxicity was evaluated using the same parameters described in the oral studies (see above) with the addition of sperm morphology and vaginal cytology (NTP, 1990).

In mice, terminal body weight was significantly decreased for the females exposed to 94, 611, and 1,104 ppm and for the males exposed to 611, 1,104, and 2,311 ppm toluene. No abnormal hematological or biochemical variations were noted for treated mice. The average testis to body weight ratio in male mice exposed to 94 and 1,104 ppm toluene was significantly increased compared to control values. Additional effects observed at higher concentrations were dyspnea, ataxia, tremors, prostration, excessive ocular discharge, increase in liver to body weight ratio, necrosis of the liver, spleen, thymus, and mesenteric lymph nodes, and death (NTP, 1990). Based on the significant reduction in terminal body weight, along with organ weight changes, a LOAEL of 94 ppm for male mice was derived. The adjusted dose for exposure at 94 ppm was 603 mg/kg-day (using 0.0316 kg bw, 0.053 m^3/day vbr) for male mice.

Brain, liver, lung, heart, and kidney to body weight ratios were significantly lower than control values in male rats exposed to 2,301 or 2,926 ppm toluene. No histological changes attributable to toluene exposure were observed in any treated rats. Fourteen-week body weights of male and female rats exposed to 2,301 and 2,926 ppm toluene were significantly lower than control values. Additional effects observed at higher concentrations were decreased liver and heart to body weight ratios.

Hsieh et al. (1989) investigated potential immunological effects of toluene administered in drinking water of mice. Male CD-1 mice were exposed to 0, 17, 80, or 405 mg/L toluene in drinking water for four weeks. The doses correspond to 0, 5, 22, and 105 mg/kg bw-day. The authors concluded that there were no hematotoxic effects although there were some consistent alterations in immune parameters generally at the highest dose level, which was also the dose that corresponded with significantly increased liver weights (hepatomegally) and significantly decreased thymus weights. The authors observed that effects of suppressed humoral and cellular immunity and decreased interleukin-2 synthesis at the high dose level were accompanied by the decrease in thymus weight, and that thymus involution is consistent with the impairment of T-cell function (Hsieh et al., 1989). From this drinking water study, we identified a subchronic NOAEL of 5 mg/kg body weight per day on the basis of liver and thymus weight changes.

Hsieh et al. (1990) exposed mice for 28 days to toluene in drinking water and monitored resultant changes in brain biogenic monoamines and their metabolites at varied dosage levels. Principal among the results was an increase of noradrenaline in the hypothalamus (Hsieh et al., 1990). The study is described in greater detail in the animal neurotoxicity section.

Poon et al. (1994) investigated the inhalation toxicity of methanol and toluene separately and combined, over a 28-day exposure in rats. The authors exposed weanling Sprague-Dawley rats, both sexes, to 30 and 300 ppm toluene vapors for six hours/day, five days/week for four weeks. In males, slightly increased liver and heart weights were found at the lower dose level, but not at the upper dose level, with a resulting LOAEL for the study calculated as 31.2 mg/kg/day (assuming 0.076 m^3 daily breathing volume and 0.050 kg body weight for the male weanling rats. This LOAEL value is equivocal, however, as a dose-response relationship was not established for the liver and heart weight changes, with the higher dose level not yielding an organ weight change effect (Poon et al., 1994).

Miyagawa et al. (1995) studied the effects of exposure to toluene in rats via inhalation to 600 ppm of toluene for 50 days in rats. Sixteen Charles River rats were exposed to the vapor and 16 rats breathed clean filtered air. Thirteen to 20 days following the end of exposure, the animals previously exposed to toluene made fewer reference memory errors which were measured as travel down incorrect arms of test maze (Miyagawa et al., 1995).

Genetic Toxicity

Numerous studies have shown that toluene is not mutagenic in bacteria, both in the presence or absence of S-9 hepatic enzyme activation system. Toluene did not elicit significant mutagenic responses in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 (Bos et al., 1981; McGregor, 1994). Similar results were obtained with *Saccharomyces cerevisiae* strains D7 and D4 and in E. coli test material strains W3110 and P3478 (Fluck et al., 1976; U.S.EPA, 1987). Toluene failed to increase the frequency of sex-linked, recessive lethal mutations in *Drosophila melanogaster* (Donner et al., 1981).

Haley (1987) reported increased incidents of chromosomal aberrations in the bone marrow cells of rats exposed to 112 ppm toluene by inhalation. However, Donner et al. (1981) exposed male Wistar rats to 300 ppm toluene by inhalation and reported no evidence of increased chromosomal aberrations. Mohtashamipur et al. (1985) reported a dose-dependent increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow cells of mice that received intraperitoneal injections of 433 to 867 mg/kg toluene. Gad-El Karim et al. (1986) reported that single oral doses of 860 mg/kg toluene were not clastogenic in Swiss CD-1 mice (Haley, 1987; Mohtashamipur et al., 1985; Gad-El Karim et al., 1986).

Notwithstanding weak or equivocal evidence, toluene is apparently not genotoxic in microbial or mammalian systems (Environment Canada, 1992; McGregor, 1994; Meek and Chan, 1994).

Developmental and Reproductive Toxicity

Toluene is listed in 1991 as a chemical known to the State to cause reproductive toxicity based on developmental effects under Proposition 65. Studies in animals have shown a clear association of toluene exposure with developmental toxicity (Donald et al., 1991). Female CR.CD rats were exposed to 1, 100, 500, and 2,000 ppm toluene in air for six hours per day, 80 days from a time prior to mating, through lactation. A significant reduction of fetal weights from dams exposed to 2,000 ppm toluene in the air was reported. A reproductive NOAEL of 500 ppm is derived from

this study. The adjusted dose for 500 ppm toluene in air for six hours per day exposure is estimated be 112.5 mg/kg-day (IRDC, 1985).

Fetal skeletal retardation in rats was reported in several rat developmental toxicity studies. In one study, CFY dams exposed to 266 ppm toluene, eight hours per day, on days one through 21 of gestation exhibited significantly greater incidence of fetal skeletal retardation than the controls (Hudak and Ungvary, 1978). Dams exposed to 399 ppm toluene continuously on days one through eight of gestation also had a significantly elevated level of fetal skeletal retardation, although the control group to which they were compared did not undergo the same treatment regimen (Hudak and Ungvary, 1978). In the same study, increases in the numbers of ribs and fused sternebrae of fetuses were reported for exposure to dams at 399 ppm toluene, on days nine through 14 of gestation. In another study, CFY dams exposed to 266 ppm toluene continuously from days seven through 14 were reported to have an increased incidence of fetal skeletal retardation (Tatrai et al., 1980).

Immunotoxicity

Hsieh *et al* (1989) studied the effects of toluene on various parameters of immunological responsiveness in CD-1 mice exposed to 0, 17, 80 and 405 mg/liter toluene in drinking water for 28 days. At the highest dose of 405 ppm, there was a significant increase in liver and decrease in thymus weights, decrease in plaque forming cells (PFC)/10^{-6} spleen cells and per spleen to sheep red blood cells, IL-2 production as measured by ^{3}H-thymidine incorporation in IL-2 dependent HT-2 cell line and proliferative response to concanavalin-A, lipopolysaccharide and pokeweed mitogens. Mitogen responsiveness and IL-2 activity measured in units based on probit transformation was also significantly reduced in the 80 ppm dose group in this study. In other immune function studies with toluene reported by Hsieh et al., (1989) either no effect was observed on mitogen responsiveness at 80 or 325 ppm dose level (1990) or reduced only at the highest dose of 405 ppm (1991) dose level suggesting that toluene suppressed the immune function parameters only at the high doses. Also, proliferative response to mitogen alone is not a good predictor of immunotoxicity (Luster et al. 1992). Therefore, the NOAEL for this study is identified to be 80 ppm (22 mg/kg-day).

Aranyi et al. (1985) investigated the immunotoxicity of toluene in a pulmonary host defense assay by inhalation exposure. Mice were exposed to toluene at concentration ranging from 1 to 500 ppm for five days (three hours/day) or 20 days (three hours/day). Mice were exposed to *Streptococcus zooepidemicus* or ^{35}S-labeled *Klebsiella pneumoniae* by aerosols challenge. A significantly increased susceptibility to experimentally induced infection and reduced pulmonary bactericidal activity was observed after single exposure to toluene at ≥ 2.5 ppm, but there was a clear lack of dose-response relationship in this study. Only at the three highest concentrations (≥ 100 ppm) significantly decreased in pulmonary bactericidal activity paralleled the mortality observation. Because of discordance in two assays no NOAEL was set for this study.

Neurotoxicity

As mentioned previously in the acute toxicity section of this report, animal exposure to toluene causes such effects as EEG changes, involuntary muscle movements, reference memory changes, and behavior changes. Furthermore, exposure causes changes in concentration of neuroactive chemicals such as biogenic amines, increases in acetyl cholinesterase and decreases in choline acetyltransferase activity. In their review and evaluation of risks to human health from environmental exposure to toluene in Canada, Meek and Chan (1994) concluded that with the exception of some behavioral effects reported at very low concentrations, and biochemical effects

on the brain the significance of which is unclear, neurotoxic effects of animals have resulted only following exposure to levels greater than those reported to induce other toxic effects in subchronic studies (Meek and Chan, 1994).

Hsieh et al. (1990) exposed mice to toluene in drinking water and monitored resultant changes in brain biogenic monoamines and their metabolites at some dosage levels. Adult CD-1 mice were continuously fed drinking water *ad libitum* containing 0, 17, 80, and 405 mg/liter toluene. Following 28 days of toluene exposure via drinking water the mice were tested for endogenous levels of the biogenic amines norepinephrine, dopamine, serotonin, and their respective metabolites. Most notable among the results was that in the hypothalamus, norepinepherine concentrations increased by 51, 63, and 34% in groups dosed respectively with 17, 80, and 405 of mg/liter toluene in drinking water (Hsieh et al., 1990).

Chronic Toxicity

Three lifetime studies of toluene in animals were available, none of which is adequate to derive a NOAEL. The study conducted by Maltoni et al. (1985) applied only one dose at 500 mg/kg by gavage to Sprague-Dawley rats and evaluated only the neoplastic changes without chronic toxicity measurements. The NTP (1990) two-year inhalation study also measured body weight changes and carcinogenicity. The only non-neoplastic change observed was acute nasal mucosa inflammation at both 600 and 1,200 ppm applied to female rats through inhalation and this change is not a measurement for chronic toxicity.

The Chemical Industry Institute of Toxicology (CIIT) sponsored an inhalation bioassay in Fischer 344 rats (CIIT, 1980). The study used six-week-old rats at 120 per sex, per exposure level. The animals were exposed to 30.1, 99.7, or 299 ppm toluene of 99.98% purity for six hours per day, five days per week for 24 months. Identical groups of rats were exposed to clean air as controls. Five animals per sex were killed at months six and 12, and 20 per sex were sacrificed at month 18. All remaining animals were killed at the end of the study. Tissue sections from the control and treated animals were examined histologically. No changes in either urinalysis or histological lesions were observed in treated rats compared with controls, although transient changes in hematocrit and corpuscular hemoglobin were observed in female rats at 99.7 and 299 ppm. This study failed to test for effects at the maximum tolerated dose (Meek and Chan, 1994; IRIS 1997).

Two six-month studies of exposure of animals to toluene were performed. In one study, groups of 27 to 30 CFY rats per sex were exposed by inhalation to 1,000 mg/m^3 (260 ppm) toluene in air (purity not stated), six hours per day, five days per week for six months (Ungvary et al., 1980). Eight to 10 rats per sex were sacrificed at months one, three, and six. An unexposed control group was observed for the same time periods. Toxicity was evaluated according to body weight gain, organ weights, organ histology, hepatic cytochrome P-450 concentrations, aniline hydroxylase and aminopyrine N-demethylase activities, protein content, serum glutamine-oxaloacetic transaminase and glutamic-pyruvic transaminase activities, and bromosulphalein retention. In addition, the liver was examined histologically.

A significant decrease in body weight gain and an increase in relative liver weight were observed in treated female rats. In addition, the concentration (per unit liver weight) of cytochrome P-450 increased in a dose-dependent manner. The bromosulphalein retention time increased significantly in both male and female rats. No gross or histological changes were attributed to toluene inhalation at either exposure level; however, hepatic changes indicative of a

compensatory reaction in the liver was observed. Therefore, a LOAEL of 1,000 mg/ m^3 (260 ppm) can be assumed from this study. For male (using 0.516 kg bw; 0.328 m^3/day vbr) and female (using 0.308 kg bw; 0.223 m^3/day vbr) rats, the adjusted doses at this level were calculated to be 114 and 129 mg/kg-day, respectively.

In a second six-month study, Miyake et al. (1983) exposed 10 male Wistar rats (six months old) to 1,027, 3,926, or 6,965 ppm toluene in air, one hour per day, six days per week, for a total of 154 exposures. A similar group of untreated rats were used as controls. Performance on several behavioral tests was used to determine CNS toxicity. The behavioral tests, administered three to four days after the termination of exposure, were Fixed-Ratio 1 and Fixed-Ratio 30 (operant conditioning chambers), wheel running (spontaneous activity), open field (emotionality and exploratory behavior), and differential responding of low rates in a 12-second schedule (DRL-12). Following the study, histological evaluation of the CNS, lung, liver, and kidney tissues was conducted for animals exposed to 3,926 or 6,965 ppm (Miyake et al., 1983).

It was reported that following exposure to 1,027 ppm toluene, the rats appeared depressed and did not respond to auditory stimuli. At 3,926 ppm, the rats were hyperexcitable during exposure. Hyperexcitability followed by mild anesthesia and ataxia was observed in rats at 6,965 ppm. All animals recovered from these effects within 10 minutes after exposure. The only behavioral test in which there was a significant change in the response of the treated animals was the DRL-12, in which exposure was associated with significantly higher responses compared to the control animals. Also, the percent of reinforced responses was significantly lower for exposed animals. These changes indicated a slowing in the acquisition of timing behavior and, according to the investigators, reflected CNS toxicity induced by toluene exposure. No gross or pathological lesions were observed at sacrifice. Based on these results, a LOAEL of 1,027 ppm toluene was assumed for risk assessment (Miyake et al., 1983). The adjusted dose for male rats (using 0.348 kg bw; 0.244 m^3/day vbr) at this level, which were also corrected for 24-hour exposures, seven days per week, was calculated to be 98.9 mg/kg-day.

Carcinogenicity

Toluene has not been tested in a standard oral cancer bioassay. In one study, Maltoni et al. (1985) exposed 80 Sprague-Dawley rats to 500 mg/kg toluene in olive oil by gavage, five days per week for two years. The results were suggestive of an association of toluene exposure with an increase in the total number of hemolymphoreticular neoplasms (Maltoni et al., 1985). The study had limitations, however, due to poor statistical analyses, inadequate reporting of incidence of different tumors, and administration of a single dose level, and are considered to be equivocal (Meek and Chan, 1994).

In contrast to the findings of Maltoni et al. (1985), the results of the two available two-year inhalation bioassays indicated no evidence of carcinogenicity induced by toluene exposure. One study was sponsored by CIIT (1980) in Fischer 344 rats. In this study, six-week old rats were exposed to 30.1, 99.7, or 299 ppm toluene (99.98% pure), six hour per day, five days per week for two years. There was no evidence of chemically related increases in neoplasia (CIIT, 1980).

The other study was sponsored by NTP (1990). The NTP study was conducted by exposing groups of 60 Fischer 344 rats of each sex to 600 or 1,200 ppm toluene, six and half hours per day, five days per week. Groups of 60 B6C3F1 mice of each sex were exposed to 120, 600, or 1,200 ppm on the same schedule. No chemically related increases in neoplasms were observed (CIIT, 1980).

On the basis of the available data, especially the NTP (1990) study, there is no clear evidence upon which to base a decision on carcinogenicity from either sex of rats and mice (Meek and Chan, 1994; McGregor, 1994; NTP, 1998).

Toxicological Effects in Humans

As a widely used chemical of commercial importance as well as a drug of human abuse, there is much general information in the literature about toxic effects of toluene exposure. Unfortunately, epidemiological studies of occupationally exposed individuals as well as cases of intentional abuse generally involve exposure to complex mixtures with toluene as the principal constituent (Meek and Chan, 1994).

Acute Toxicity

Acute exposures to 100 to 400 ppm toluene resulted in respiratory tract and conjunctival irritation (Carpenter et al., 1944; Biscaldi et al., 1981; Baelum et al., 1985; Wahlberg J, 1984). Human subjects exposed to 100 ppm toluene for six hours reported headache, dizziness, and feeling of intoxication (Andersen et al., 1983).

Toxicity associated with short-term human overexposures to toluene are typically reported in clinical case studies. Exposure to high levels of toluene frequently resulted in narcotic and anesthetizing effects in humans (Brugnone et al., 1983; NIOSH, 1984; Winek et al., 1968). Although complete recovery from toluene-induced comas was reported (Brugnone et al., 1983), in some cases of extreme overexposure, both permanent or prolonged comas and death have ensued (Winek et al., 1968).

Alteration of CNS function after acute exposure was reported in studies of human subjects inhaling toluene (von Oettingen et al., 1942; Carpenter et al., 1944; Gamberale and Hultingren, 1972; Andersen et al., 1983; Baelum et al., 1985). In these reports, dose-dependent effects such as drowsiness, fatigue, and headache were observed at 50 to 800 ppm toluene. At higher doses, muscle weakness, incoordination, nausea, insomnia, and dilated pupils were also noted. Decreased reaction time and perceptual speed were observed (Ogata and Fujii, 1979; Gamberale and Hultingren, 1972; Dick et al., 1984). Six female workers at an electromechanical factory accidentally inhaled toluene vapors experienced nausea, dizziness, and headaches immediately after exposure (Biscaldi et al., 1981). For five of the six women, abnormal EEGs were also reported.

In cases of toluene abuse, inhalation of toluene was rapidly followed by a burst of activity such as running or frenzied behavior (Bass, 1970; Winek et al., 1968; Chikasue et al., 1985). For fatal intoxication, severe cardiac arrhythmia resulting from anesthesia and intensified by hypercapnia (high pCO_2), stress, physical activity, or a combination of these were the presumed causes of death.

Burbacher (1993) summarized “occupational or short-term neurotoxic effects” of toluene exposure as reduced manual dexterity, reduced vigilance, short-term memory loss and disruptions in perception. These effects are noticed at air concentrations above 100 ppm (Burbacher, 1993)

Subchronic Toxicity

Few subchronic data exist for which human exposure is to toluene in known pure form.

Genetic Toxicity

Richer et al. (1993) exposed five healthy white humans to 50 ppm toluene for seven hours per day over three consecutive days. Blood samples were taken and compared with control samples drawn before the exposures began. Three different cytogenetic endpoints were evaluated using peripheral blood lymphocytes, 1) numbers of sister chromatid exchanges, 2) cell cycle delay, and 3) cell mortality. No significant effects were observed. The authors concluded that exposures to low levels of toluene do not pose any potential mutagenic threat to humans (Richer et al., 1993).

Developmental and Reproductive Toxicity

Taskinen et al. (1994) studied frequency of spontaneous abortions among 535 women working in laboratories. The study also included congenital malformations among the offspring of 141 women, and birth weights of the children of 500 women working in laboratories in a retrospective case-referent study. Significant associations with spontaneous abortions were found for exposure to toluene with an odds ratio reported as 4.7 at a 95% confidence interval (Taskinen et al., 1994).

Arnold et al. (1994) described toluene embryopathy resulting from maternal abuse of toluene. The authors reviewed 35 case records of deliveries with antenatal exposure to toluene. There were three perinatal deaths, and of the survivors, 42% were delivered prematurely, 32% had microencephaly, and 52% had low birth weight. Birth weight, length, and head circumference were significantly less than a cohort group closely matched for gender, race, and socioeconomic status (Arnold et al., 1994).

Neurotoxicity

The most common subchronic and chronic effects of toluene on the CNS in humans are cerebellar and cerebral disease, accompanied by diffuse encephalopathy, optic neuropathy, and sensoneural hearing loss. Impairment of psychomotor functions as a result of toluene exposure has also been noted.

Several studies of long-term toluene exposure to humans confirmed that CNS effects are the most predominant concerns associated with toluene exposure. In a study of 1,000 employees exposed to 50 to 1,500 ppm toluene for up to three weeks, 100 complained of headache, lassitude, loss of appetite, slight impairment of coordination and reaction time, and momentary losses of memory (Wilson, 1943). These effects were intensified in workers exposed to levels above 500 ppm. Significant decreases in reaction time were reported for 34 rotogravure printers who were exposed to 50 to 150 ppm toluene for an average of 16.3 years (Iregren, 1982). In another study, disturbances in memory, thinking, and activity were reported in 21% of printers and 40% of printers' (110 total) helpers exposed to approximately 300 and 430 ppm toluene, respectively (Muchinger 1964, as cited by U.S. EPA 1990). Abnormal EEG were also observed in workers exposed to greater than 260 ppm toluene (Rouskova, 1975). Male rotogravure printers chronically exposed to approximately 117 ppm toluene complained of numbness, headache, dizziness, insomnia, cognitive and cerebellar disturbances, memory loss, and EEG and neuropsychological abnormalities (Juntunen et al., 1985).

Occupational exposure to toluene has also been associated with adverse effects on peripheral nerves and neuromuscular function (Matsushita et al., 1975; Struwe and Wennberg, 1983; Seppalainen et al., 1978). An abnormal patellar reflex and a decrease in grasping power were found in 14 of 38 female shoemakers exposed to 60 to 100 ppm toluene vapor for an average of three years and four months (Matsushita et al., 1975). Coscia et al. (1983) examined 53 workers in the rotogravure industry exposed to 110 to 420 ppm toluene (average 295 ppm) for an average of 11.2 years and reported that 15 had prevalently bilateral, symmetric vestibular hyporeflexia (Coscia et al., 1983). In contrast, no significant difference in the mean values for motor and sensory conduction velocities, nor in motor distal latencies from nerves in the upper and lower extremities was found in 59 car painters exposed for 1 to 40 years to a mixture of organic solvents containing a mean concentration of 30.6 ppm toluene (Seppalainen et al., 1978). However, abnormalities in individual maximal motor and/or sensory conduction velocities and/or in motor distal latencies were present in 20% of the car painters.

Foo et al. (1993) measured neurobehavioral effects of toluene on humans exposed chronically in an occupational setting. Thirty female electronics factory workers, aged 18-41, were exposed to an average of 341 mg/m^3 for an average of 5.7 years. Exposures were five days/week, nine hours/day. The results were compared with unexposed controls aged 18-48. The authors conducted neurobehavioral tests on short-term memory, visual motor speed, and manual dexterity. The authors concluded that adverse neurobehavioral performance was associated with exposure to toluene and solvent mixtures containing toluene. The authors also concluded that due to the fact that the neurobehavioral effects were mainly related to intensity of exposure and less affected by duration of exposure; and, that the effects are "probably highly reversible" (Foo et al., 1993).

The signs of neurotoxicological damage observed in chronic abusers are more severe than those occupationally exposed to toluene, due to the high levels of exposure typical of toluene abusers. The toluene concentration in respired air during abuse may be 10,000 ppm, 50 times higher than the American Conference of Governmental Industrial Hygienists' (ACGIH) suggested maximum allowable concentration of 200 ppm for the workplace (Press and Done, 1967). Numerous case reports suggest that toluene drug abuse in humans results in severe CNS toxicity.

One patient with a 14-year history of toluene abuse exhibited tremors of hands and feet, slowed movement of the upper extremities, and rebound phenomena in both arms and legs (Grabski, 1961; Knox and Nelxon, 1966). Headaches, inappropriate speech, brief episodes of memory loss, and abnormal EEGs were reported in a patient with a 10-year history of toluene abuse (Satran and Dodson, 1963). Atrophy of the midbrain and cerebrum was reported in a male who had abused toluene for two years (Sasa et al., 1978). Acute encephalopathy was reported in 20 children between the ages of 8 and 14 who were hospitalized as a result of toluene abuse (King, 1982). These patients presented with euphoria, visual hallucinations, suicidal inclination, drowsiness, convulsions, coma, headache, vomiting, dysarthria, and ataxia. Three patients who were abusing a toluene-based glue exhibited convulsions involving all four limbs (Helliwell and Murphy, 1979). Severe multifocal CNS alternations with evidence of cerebral cortical, cerebellar, and brainstem atrophy were evident in four individuals who abused toluene daily for three to seven years (Lazar et al., 1983).

Peripheral neuropathy or paresthesia occurred in 2 of 25 patients hospitalized as a result of inhaling paint vapors containing toluene (Streicher et al., 1981). Subclinical sensory neuropathy, as evidenced by nerve conduction studies, was observed in a patient with a five-year history of glue sniffing (Ehyai and Freemon, 1983). Optical neuropathy and eye twitching were also

reported in individuals following long-term toluene abuse (Keane, 1978; Ehyai and Freemon, 1983; Grabski, 1961; Sasa et al., 1978; Lazar et al., 1983). Losses of high-frequency hearing acuity and near deafness were reported in individuals exposed to high levels of toluene over a long period of time (Ehyai and Freemon, 1983; Boor and Hurtig, 1977).

Byrne and Kirby (1990) observed more than 20 chronic abusers of toluene-containing solvents and found a high incidence of paranoid psychoses, including pronounced states of confusion with fluctuating states of consciousness. A number of these patients failed to recover from their psychoses, had a higher than expected incidence of temporal lobe epilepsy, and a documented fall in I.Q (Byrne and Kirby, 1990).

Emmen et al. (1995) studied 131 toluene-exposed workers and compared them to 69 non-exposed workers, as they were subjected to a battery of neurobehavioral tests. The authors tested memory, reaction time, attention, perception, and vision tracking performance. In addition, subjective symptoms were evaluated using a standard neurotoxicity symptom questionnaire. The results demonstrated significant delays in perception in the exposed group as well as higher prevalence of subjective complaints regarding memory, sleep disturbances, paresthesia, and reduced neuromuscular strength among the toluene-exposed workers (Emmen et al., 1995).

Chronic Toxicity

Several studies of neurotoxicological effects of chronic toluene exposure to humans were summarized in the preceding section on neurotoxicity. These studies include those reported by Byrne and Kirby (1990), Foo et al (1993), Emmen et al. (1995), and Iregren (1992).

Hepatotoxicity was also reported following toluene abuse or occupational exposure to toluene. Hepatomegaly was reported in individuals chronically exposed to toluene (Greenburg et al., 1942; Grabski, 1961). Liver biopsy of a printing trade worker exposed to toluene for 14 years revealed diffuse fatty degeneration and focal necrosis accompanied by an increase in alanine aminotransferase activity (Dossing et al., 1983). Jaundice and reversible elevations in serum bilirubin and alkaline phosphatase (ALP) were reported in a patient with a three-year history of glue sniffing (O'Brien et al., 1971).

In contrast, several investigators have reported normal liver function in patients who chronically sniffed glue (Massengale et al., 1963; Satran and Dodson, 1963; Powars, 1965; Taher et al., 1974; Boor and Hurtig, 1977; Ehyai and Freemon, 1983). Capellini and Alessio (1971) (as cited by U.S. EPA, 1990) reported normal liver function in 17 workers exposed to 80 to 160 ppm toluene in a V-belt manufacturing plant. Suhr (1975) (as cited by U.S. EPA, 1990) reported elevated hepatic activities and hepatomegaly in a group of 100 rotogravure printers, but these parameters were not significantly different from a group of 100 unexposed workers (Capellini and Alessio, 1971; Suhr, 1975).

Renal dysfunction was reported in several case studies of toluene abuse. The most common symptoms of renal dysfunction are pyuria, hematuria, and proteinuria (Massengale et al., 1963; Sokol and Robinson, 1963; Barman et al., 1964; Press and Done, 1967; O'Brien et al., 1971; Streicher et al., 1981). Metabolic and renal tubular acidosis were also reported in individuals who abused toluene (Taher et al., 1974; Fischman and Oster, 1979; Bennett and Forman, 1980; Kroeger et al., 1980; Moss et al., 1980; Russ et al., 1981; Streicher et al., 1981; Batlle et al., 1988; Goodwin, 1988; Patel and Benjamin, 1986). Although renal dysfunction is not generally associated with occupational exposure to toluene (Greenburg et al., 1942) (Matsushita et al., 1975; Nielsen et al., 1985) Bosch et al,. 1988 described a case of focal segmental glomerulosclerosis in a 60-year-old man who was occupationally exposed to toluene for 40 years (Bosch et al., 1988).

Cardiac toxicity was described in several reports of toluene abuse, but it was not observed consistently in epidemiological or experimental studies. For example, no difference in ECG was observed in rotogravure printers with histories of long-term exposure to toluene versus age- and sex-matched controls (Juntunen et al., 1985). On the other hand, Streicher et al. (1981) reported cardiac arrhythmias or abnormal ventricular contractions in 5 of 25 patients who abused toluene-containing paint. Enlargement of the heart, dilation of the ventricles, and a parasystolic murmur were observed in a 15-year-old boy who sniffed a toluene-based glue intermittently for two years (Wiseman and Banim, 1987).

Adverse hematological and hematopoietic effects have been reported following occupational, accidental, and abusive exposures to toluene. These effects, however, were not always consistent (Friborska, 1973; Greenburg et al., 1942; Tahti et al., 1981; Forni et al., 1971; Powars, 1965; Matsushita et al., 1975; Bosch et al., 1988; Capellini and Alessio, 1971). Normal blood parameters were reported in patients who chronically abused glue containing toluene (Satran and Dodson, 1963; Taher et al., 1974; Boor and Hurtig, 1977; Bennett and Forman, 1980; Ehyai and Freemon, 1983).

Carcinogenicity

Epidemiological studies examining the possible association between toluene exposure and cancer were not found in the available literature. Toluene was mentioned as an exposure in four case-control studies involving several anatomical sites of cancer; however, the exposures involved multiple chemical exposures and the results could not be evaluated with regard to toluene itself (IARC, 1989). The International Agency for Research on Cancer (IARC) determined that toluene is not classifiable as to its carcinogenicity to humans (IARC, 1989).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

In 1991, U.S. EPA calculated the Drinking Water Equivalent Level (DWEL) for lifetime exposure to toluene to be 7 mg/L as a function of the oral reference dose (RfD), of 0.223 (rounded to 0.2) mg/kg-day U.S. EPA, 1990). The DWEL is a lifetime exposure concentration protective of adverse, non-cancer health effects under the assumption that all of the exposure to a contaminant is via drinking water (U.S. EPA, 1998). U.S. EPA considered the following animal oral studies for its derivation of the toluene DWEL (U.S. EPA, 1990)

Wolf et al. (1956) found no gross or histological signs of toxicity in rats treated orally with 590 mg/kg-day, five days/week, for six months, thus establishing an early NOAEL of oral toluene intoxication.

NTP (1990) orally intubated F334 rats and B6C3F1 mice. Male rats, the more sensitive sex and species, were dosed at toluene levels in corn oil, of 312, 625, 1,250, 2,500 or 5,000 mg/kg-day, for five days per week for 13 weeks. Liver and kidney weight changes were reported at $\geq$ 625 mg/kg toluene-day. The resulting NOAEL was reported as 312 mg/kg-day; and, adjusting for five days exposure per week, the NOAEL is 223 mg/kg-day. From the NTP paper, U.S. EPA selected the adjusted NOAEL of 223 mg/kg-day, from which it calculated its reference dose of 0.2 mg/kg-day, and subsequently, its DWEL of 7 mg/L toluene in drinking water. U.S. EPA's MCL of 1 mg/L toluene in drinking water uses the same NOAEL based on the same study.

OEHHA had earlier considered the NTP 13-week study to be the most appropriate work upon which to base its Recommended Public Health Level (RPHL) (OEHHA, 1992). After estimating water intake of 11.2 liter equivalents/day, the result of the otherwise standard calculation for the public health-protective calculation was divided by an additional uncertainty factor of two to account for the possibly more sensitive effects of neurotoxicity. The calculated RPHL value for toluene was 0.15 mg/L/day. Because of the difficulty of assessing neurotoxic effects quantitatively, however, neurotoxicity was not used in the calculation of the PHG.

We currently view the study by Hsieh et al. (1989) as the most appropriate study from which to derive a NOAEL for a public health goal for toluene. The authors investigated potential immunological effects of toluene in drinking water of mice. Male CD-1 mice were exposed to 0, 17, 80, and 405 mg/L toluene in drinking water for four weeks. The doses correspond to 0, 5, 22, and 105 mg/kg bw-day. Although exposure duration was considerably shorter in the Hsieh (1989) study (four weeks) than in the NTP (1990) study (13 weeks), both studies were subchronic in duration. Dosing was daily in the 28-day study versus five days/week in the 13-week study.

As with the previously mentioned NTP study, organ weight changes (an increase in liver and a decrease in thymus weights) were reported by Hsieh et al. (1989). The observed effects of suppressed humoral and cellular immunity and decreased IL-2 syntheses were concordant with the decrease in thymus weight (Hsieh et al. 1989). Importantly, 105 mg/kg bw-day represents a LOAEL (for the same effects) which is lower than the previously established NOAEL of 223 mg/kg bw-day (U.S. EPA, 1990; OEHHA, 1992). Accordingly, the previous NOAEL, being higher than a LOAEL, is no longer the most appropriate value for use in PHG determination. Hence, from the Hsieh (1989) drinking water study, we identified a subchronic NOAEL of 22 mg/kg body weight per day on the basis of absence of liver and thymus weight changes and related immunotoxic effects; and, we use this value in the calculation of the public health goal.

Toluene is not recognized as a carcinogen, and a risk assessment examining carcinogenic effects is not undertaken.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncancer toxicants must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, and for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

Noncancer Effects

From a study in which toluene was administered to mice via drinking water (Hsieh et al., 1989), we identified a subchronic NOAEL of 22 mg/kg-day and a LOAEL of 105 mg/kg-day on the basis of liver weight increases, thymus weight decreases, and related immunotoxic effects. The calculation of the public health-protective concentration (C, in mg/L) for toluene follows a general formula for noncancer endpoints:

$$C = \frac{NOAEL \times RSC \times BW}{UF \times L/day} = PHG \text{ in mg/L}$$

where,

NOAEL	=	No-observed-adverse-effect-level (22 mg/kg-day).
RSC	=	Relative source contribution of 40% (0.4) because volatile chemicals such as toluene are less likely to be found in food and soil.
BW	=	Body weight for an adult male (70 kg)
UF	=	Uncertainty factor of 1,000 (10-fold for inter-species variation, 10-fold for human variability, 10-fold to account for the use of a subchronic study for determining a lifetime value)
L/day	=	Volume of drinking water consumed by an adult (4 L/day). The default is 2L/day, however the higher value accounts for additional inhalation exposure from various uses of drinking water, such as bathing.

Therefore,

$$C = \frac{22.0 \text{ mg/kg-day} \times 0.4 \times 70 \text{ kg}}{1{,}000 \times 4 \text{ L/day}}$$

$$= 0.154 \text{ mg/L, rounded} = 0.15 \text{ mg/L (150 ppb)}$$

The PHG for toluene in drinking water is therefore 0.15 mg/L (150 ppb).

For comparison, U.S. EPA's DWEL calculation of 7 mg/L (7,000 ppb) assumes that 100% of the human exposure to toluene derives from drinking water. The RSC is an assumption of the percentage of exposure we would receive via drinking water relative to other potential sources such as food and air. People are not normally exposed to toluene via drinking water; however, relative to other routes, such as air, food, and soil, water would be the predominant medium of toluene exposure. Volatile chemicals such as toluene are less likely to be found in food and soil. An RSC value of 40% exposure from drinking water is most appropriate for toluene.

RISK CHARACTERIZATION

Toluene is a volatile, reactive chemical which is nearly insoluble in water and generally does not persist in the environment. Toluene is typically not found in California drinking water (DHS, 1998). Significant exposures of toluene to humans are usually occupational, such as rotogravure printing operations, or by intentional inhalation as a drug of abuse. The acute toxicity of toluene is relatively low with rat oral LD_{50}s ranging between 2.6 and 7.5 grams/kg body weight/day (Meek and Chan, 1994). Absorption of toluene in animals via inhalation (the most likely route for human exposure) proceeds more rapidly than toluene absorption via the gastrointestinal tract. There was no clear evidence of carcinogenicity from an NTP rat and mouse toluene inhalation study (NTP, 1990; McGregor, 1994; NTP, 1998).

The PHG is based on a subchronic drinking water study in mice (Hsieh et al., 1989) in which the authors investigated potential immunological effects of toluene in drinking water of mice. Male CD-1 mice were exposed to 0, 17, 80, or 405 mg/L toluene in drinking water for four weeks.

The doses correspond to 0, 5, 22, and 105 mg/kg bw-day. The authors concluded that there were no hematotoxic effects although there were some consistent alterations in immune parameters generally at the highest dose level, which was also the dose that corresponded with significantly increased liver weights (hepatomegaly) and significantly decreased thymus weights. The authors suggest a relationship between the decrease in thymus weights and the observed effects of suppressed humoral and cellular immunity and decreased interleukin-2 synthesis at the 105 mg/kg bw-day dose level; and further, that thymus involution is consistent with the impairment of T-cell function. Importantly, 105 mg/kg bw-day represents a LOAEL, which is lower than the previously established NOAEL of 223 mg/kg bw-day. Accordingly, the previous NOAEL, being higher than a LOAEL, is no longer the most appropriate value for use in PHG determination. Hence, in the Hsieh (1989) drinking water study, we identified a subchronic NOAEL of 22 mg/kg body weight per day on the basis of absence of liver and thymus weight changes and related immunotoxic effects; and, we use this value in the calculation of the public health goal.

OTHER REGULATORY STANDARDS

The current U.S. EPA MCL for toluene is 1 mg/L (U.S. EPA, 1996). In 1992 OEHHA a RPHL of 150 ppb (OEHHA, 1992). The following table includes selected national and state regulations and guidelines for comparison to the recommended PHG.

Table 4. Selected Guidelines And Regulations For Toluene

Agency	Standard or Criterion	Level	Comment
Cal/EPA OEHHA	RPHL (1992) (recommended public health level)	0.15 mg/L	based on NTP subchronic data
OEHHA	Acceptable daily intake level for reproductive toxicants	7,000 mg/day (1.7 mg/L) based on 4L	Based on developmental toxicity
ATSDR	oral MRL (minimum risk level), intermediate duration	0.02 mg/kg-d	based on neurotransmitter level changes, mouse brain tissues
NIOSH	REL (recommended exposure level)	100 ppm	recommended occupational inhalation level
	STEL (short-term exposure level)	150 ppm	
OSHA	PEL (permissible exposure limit)	200 ppm	occupational. inhalation level
U.S. EPA	MCL (maximum contaminant level)	1 mg/L	national drinking water standard
U.S. EPA	MCLG (max. contaminant level goal)	1 mg/L	goal, includes safety margin
U.S. EPA	Lifetime Health Advisory	1 mg/L	lifetime health-based reference level
U.S. EPA	DWEL (drinking water equivalent level)	7 mg/L	non-cancer protective level
ACGIH	TLV-TWA (threshold limit value-time weighted average)	100 ppm	occupational inhalation

Table adapted from (ATSDR, 1994; NIOSH, 1994; U.S. EPA, 1995; U.S. EPA, 1996)

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