Public Health Goal for
ETHYLBENZENE
in Drinking Water

Prepared by
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PREFACE

Drinking Water Public Health Goal of the
Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. 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 adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus 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 scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
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 periodically 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. For this reason PHGs are only one part of the information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden 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 developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. 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 environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.

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SUMMARY

A Public Health Goal (PHG) of 0.3 mg/L (300 ppb) is developed for ethylbenzene in drinking water. U.S. EPA determined that ethylbenzene is not classifiable as to human carcinogenicity (Group D). Therefore, the PHG calculation is based on noncarcinogenic effects observed in experimental animals. The National Toxicology Program (NTP) study cited in the development of the PHG provides evidence of hepatotoxicity in mice exposed to 250 ppm ethylbenzene in air for two years. This type of effect is consistent with other reports on the toxicity of ethylbenzene. A no-observed-adverse-effect-level (NOAEL) for hepatotoxicity was determined to be 75 ppm from the NTP study, corresponding to a daily dose of 49 mg/kg. For the calculation of the PHG, factors accounting for uncertainty in inter-species extrapolation, potentially sensitive human subpopulations and the potential for a severe effect (cancer) were incorporated, for a cumulative uncertainty factor of 1,000. Based on these considerations, OEHHA calculates a PHG for ethylbenzene of 0.3 mg/L (300 ppb).

INTRODUCTION

The purpose of this document is to develop a PHG for ethylbenzene in drinking water. In an evaluation of the available literature as of 1991, the U.S. Environmental Protection Agency (U.S. EPA) determined that ethylbenzene is not classifiable as to human carcinogenicity (Group D; U.S. EPA, 1991a). The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of ethylbenzene.

In this document, we evaluate the available data on the toxicity of ethylbenzene, with the primary focus on the literature related to oral exposures which may be most appropriate for the establishment of a PHG for drinking water. To determine a public health-protective level for ethylbenzene in drinking water, an effort was made to identify more sensitive subgroups in the general population (and if there is inadequate information to identify such groups, appropriate uncertainty factors were incorporated into the PHG). The studies which can be used to identify public health-protective levels are reviewed and evaluated.

CHEMICAL PROFILE

Ethylbenzene (phenylethane; CAS No. 100-41-4) is a colorless liquid at room temperature with the molecular formula C_8H_{10} and a molecular weight of 106.16 g/mole (4.42 mg/m^3 per ppm in air at 20°C) (chemical data from HSDB, 1997, except as noted). It has a melting point of -95.0°C, a boiling point of 136.2°C and a vapor pressure of 10 mm Hg at 25.9°C. It is minimally soluble in water (140 mg/L at 15°C), but is miscible with many organic solvents, including ethanol and ethyl ether.

Ethylbenzene has an odor which has been described as aromatic, pungent or sweet and gasoline-like (HSDB, 1997). The odor threshold has been approximated at 2.3 ppm (Amoore and Hautala, 1983), although lower values have been reported (0.09 to 0.6 ppm) (AIHA, 1989). A taste threshold in water has been estimated at 0.1 mg/L (Fazzalari, 1978).

PRODUCTION AND USE

The primary use of ethylbenzene is as a chemical intermediate in the production of styrene monomer, which accounts for more than 99% of its use (HSDB, 1997). It has been used in the manufacture of synthetic rubber, acetophenone and cellulose acetate. As an organic liquid, it also has use as an industrial solvent for insecticides and acetophenone and as a diluent in the paint industry (a replacement for benzene). Ethylbenzene is a component of gasoline (added to 2% by weight as an anti-knocking agent) and is also present in preparations of naphtha, asphalt and xylene.

Most ethylbenzene is produced by the Friedel-Crafts alkylation reaction with benzene, ethylene and an aluminum chloride catalyst and promoter (Fishbein, 1985). Production of ethylbenzene in the United States (U.S.) has been estimated at 11.76 billion pounds (1993), while 1983 estimates of ethylbenzene imports were 87 million pounds (HSDB, 1997). For the years 1982 and 1983, ethylbenzene ranked among the top 20 chemical products (Fishbein, 1985).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

The high level of production and use of ethylbenzene in industry results in the potential for contamination of air, soil and water. As a component of crude petroleum and a product of combustion, ethylbenzene is also a naturally occurring compound (Fishbein, 1985).

Air

The presence of ethylbenzene in gasoline as well as its common use as a solvent results in a significant potential for release to air. Urban air has been shown to have higher levels of ethylbenzene than rural air. Vehicle emissions have been proposed to be the major contributor to air contamination (ATSDR, 1990). Estimates of ethylbenzene in urban air have included levels up to 23.1 ppb and a range of 3 to 15 ppb ethylbenzene (Fishbein, 1985; ATSDR, 1990, citing Jonsson *et al.*, 1985). Other surveys have reported remote or rural air levels of ethylbenzene of less than 0.2 ppb and suburban and urban median concentrations of 0.6 ppb; higher estimates near roads have been reported (10 to 16 ppb) (ATSDR, 1990).

The use of consumer products containing xylene and ethylbenzene such as degreasers, insecticides, lacquers and paint removers results in the potential for exposure of the general population. Ethylbenzene has also been identified as a component of tobacco smoke. Because of the enclosed environment, indoor air estimates of ethylbenzene frequently are higher than those outdoor.

Toxic Release Inventory (TRI) data for California indicate that for the years 1987 to 1994, air releases ranged from 89,836 to 211,362 pounds (U.S. EPA, 1997). Nationwide air emissions for 1988 were estimated at 47 billion pounds (ATSDR, 1990).

Soil

Soil contamination by ethylbenzene may potentially occur through fuel spillage, solvent disposal or storage tank leakage. Of the hazardous waste sites tested for ethylbenzene contamination, 25% showed detectable levels with a geometric mean soil concentration of 67 ppb (ATSDR, 1990).

Water

Water has the potential to become contaminated by ethylbenzene from its use in industry (discharges), as a fuel component and by storage tank leakage. Drinking water supplies taken near leaking gasoline storage tanks or from surface waters have the highest potential for contamination.

Among the approximately 4% of surface water samples in which ethylbenzene has been detected, the geometric mean concentration was approximately 340 ppb (ATSDR, 1990; citing U.S. EPA, 1989). Median concentrations for surface water samples, however, were reported to be less than 5 ppb. Among the approximately 11% of ground water samples in which ethylbenzene has been detected, the mean concentration was approximately 70 ppb.

Public drinking water samples in Rhode Island were reported to have ethylbenzene levels ranging from 1 to 3 ppb (ATSDR, 1990). Likewise, water supplies in New Orleans (1974) were reported to contain 1.6 to 2.3 ppb ethylbenzene. When detected, well water sampling has generally shown higher ethylbenzene concentrations.

Food

There are some reports of measurable quantities of ethylbenzene in food products (ATSDR, 1990; citing Lovegren *et al.*, 1979). Concentrations of 0.005 to 0.013 ppm have been measured for food products such as split peas, lentils and beans.

The chemical and pharmacokinetic properties (low bioconcentration factor, rapid metabolism - see below) of ethylbenzene suggest little potential for significant bioaccumulation in aquatic organisms.

METABOLISM AND PHARMACOKINETICS

Absorption

Both oral and inhalation exposure of human subjects to ethylbenzene results in rapid absorption (NTP, 1996; citing Bardodej and Bardodejova, 1970; Climie *et al.*, 1983). Inhalation exposure of 18 human male volunteers to 100, 187, 200 or 370 mg/m^3 ethylbenzene resulted in an absorption estimate of 64% (Bardodej and Bardodejova, 1970). Inhalation exposure of rats to 1 mg/L for six hours resulted in an absorption estimate of 44%, although the possibility of dermal absorption (due to whole-body exposure) was not considered (Chin *et al.*, 1980). Six human volunteers exposed to 18, 34, 80 and 200 mg/m^3 ethylbenzene demonstrated a lung retention of 49% of the ethylbenzene vapors (Gromiec and Piotrowski, 1984).

The dermal absorption of ethylbenzene has been studied in 14 human volunteers exposed to aqueous solutions of 112 and 156 mg/L (Dutkiewicz and Tyras, 1967). The skin absorption rate was determined to be 0.12 and 0.21 mg/cm^2/hour which was described as rapid relative to other organic compounds such as benzene and styrene. Dermal absorption of liquid ethylbenzene was also estimated at 22 to 33 mg/cm^2-hour (Dutkiewicz and Tyras, 1967). Percutaneous absorption of ethylbenzene in rat skin (*in vitro*) was estimated at 105 ng/cm^2-minute (approximately 0.064 mg/cm^2-hour) (Tsuruta, 1982). Total percutaneous absorption of 3.4% of the applied dose (occluded) was estimated for ethylbenzene applied to hairless mice (Susten *et al.*, 1990).

Distribution

The low solubility of ethylbenzene in blood and moderate lipophilicity will result in rapid distribution to all tissues, including the brain. Ethylbenzene does not highly concentrate in any tissue, but reaches equilibrium within a few minutes in rapidly perfused tissues and more slowly, to a higher concentration, in fat.

Exposure of rats to radiolabeled ethylbenzene by inhalation has demonstrated distribution to the liver, gastrointestinal tract and adipose tissue (Chin *et al.*, 1980). Although the experimental design measured ethylbenzene levels within two days, distribution to these sites would be expected to be very rapid. Similarly, oral administration of radiolabeled ethylbenzene to rats resulted in distribution to the liver, kidney, intestine and adipose tissue (Climie *et al.*, 1983). Humans exposed to ethylbenzene orally or by inhalation have exhibited low levels in subcutaneous and body fat (Engstrom and Bjurstrom, 1978; Wolf *et al.*, 1977). Transplacental transport appears to occur as evidenced by the appearance of ethylbenzene in cord blood (HSDB, 1997)

Metabolism and Excretion

1-Phenylethanol (α-methylbenzyl alcohol), mandelic acid and phenylglyoxylic acid have been identified as metabolites in the urine of human subjects exposed to ethylbenzene (Bardodej and Bardodejova, 1970; Engström *et al.*, 1984). Oxidation of the side chain appeared to be the primary metabolic conversion for excretion into urine among human subjects exposed to ethylbenzene by inhalation (150 ppm), while ring oxidation accounted for only 4% of the metabolic products (Engström *et al.*, 1984). Minor metabolites identified in human urine included methylphenyl carbinol and 2-ethylphenol (Bardodej and Bardodejova, 1970).

In rats exposed to ethylbenzene by inhalation, the primary metabolites were 1-phenylethanol, mandelic acid and benzoic acid, although 11 other probable metabolites were identified. Minor metabolites identified were ω-hydroxyacetophenone, 1-phenyl-1,2-ethanediol, acetophenone, p-hydroxyacetophenone and phenylglyoxal (Engström, 1984). Metabolic products were found to be conjugated with glucuronide, sulfate and glycine. Mandelic acid and phenylglyoxylic acid were identified as minor metabolites in another study in rats and rabbits (Kiese and Lenk, 1974). As in the case of human metabolites, side chain oxidation products predominated. Differences in the metabolic products of ethylbenzene in experimental animals and humans have been reported to be minor (NTP, 1996; citing Chin *et al.*, 1980, Climie *et al.*, 1983).

In rats, urinary elimination of total identified metabolites after 48 hours accounted for 59 and 83% of absorbed doses resulting from six hour inhalation exposure to 300 and 600 ppm ethylbenzene, respectively (Engström, 1984). A minor level of respiratory elimination of unchanged ethylbenzene is also likely (HSDB, 1997). Urinary elimination of the metabolite mandelic acid from human volunteers exposed by inhalation was reported to be biphasic, with elimination half-lives of 3.1 and 24.5 hours (Gromiec and Piotrowski, 1984).

TOXICOLOGY

Toxicological Effects in Animals

Acute Effects

Estimates of the LD_{50} from oral exposure to ethylbenzene have included 5.5 g/kg (rat; Smyth *et al.*, 1962) and 3.5 g/kg (rat; Wolf *et al.*, 1956). An LD_{50} estimate from intraperitoneal exposure was 2.3 g/kg (mouse; Lewis, 1992).

Inhalation LC_{50} estimates for ethylbenzene include 4,000 ppm (four-hour, rat) (Smyth *et al.*, 1962), 8,000 ppm (one-hour, rat) (Smyth *et al.*, 1962) and approximately 8,000 and approximately 13,000 ppm (two-hour, mice and rats, respectively) (Ivanov, 1962). Symptoms among affected animals included sleepiness, leukocytosis, pulmonary congestion and hyperemia of the viscera (Yant *et al.*, 1930). Eye and nose irritation of guinea pigs has resulted from short-term exposure to 1,000 to 2,000 ppm ethylbenzene (Lewis, 1992). Higher concentrations (10,000 ppm) have resulted in tremor, ataxia and loss of consciousness and ultimately death to the guinea pigs (Lewis, 1992; ACGIH, 1991). Pulmonary irritation, decreased respiration and anesthesia were observed following 30 minute exposure of mice to ethylbenzene concentrations ranging from 410 to 9,640 ppm ethylbenzene (Nielsen and Alarie, 1982).

An LD_{50} of 15.4 g/kg was estimated in rabbits exposed dermally to ethylbenzene (Smyth *et al.*, 1962).

Three-day exposure of rats to 2,000 ppm ethylbenzene (six hours/day) resulted in significant increases in kidney and liver weight as well as the induction of hepatic cytochrome P_{450} and microsomal enzymes (Toftgård and Nilsen, 1981; Toftgård and Nilsen, 1982). Male rats exposed for three days (six hours/day) to 2,000 ppm ethylbenzene exhibited several biochemical changes, including an increased turnover of dopamine and noradrenaline in the hypothalamus and median eminence, and a 30% decrease in serum prolactin concentrations (Andersson *et al.*, 1981).

Subchronic Effects

F344 rats, B6C3F1 mice and New Zealand white rabbits (five/sex/group) were exposed to 0, 99, 382 or 782 ppm (rats and mice) or 0, 382, 782 or 1,610 ppm (rabbits) ethylbenzene for six hours/day, five days/week for four weeks (Cragg *et al.*, 1989). Among male rats, liver weight was significantly increased in the mid-dose group, while among male and female rats in the high-dose group, liver weight, liver-to-body weight ratio and liver-to-brain weight ratio were increased. Significantly increased liver weight (female mice) and liver-to-brain weight ratios (male and female mice) were observed among animals in the high-dose group. Platelet count and leukocyte count were increased among male and female rats, respectively, in the high-dose group. Neither gross nor microscopic changes in over 30 tissues collected from the animals were observed. Body weight gain was decreased among female rabbits in the high-dose group. Transient decrease in body weight gain was observed among male rabbits in the high-dose group. No clinical chemistry effects were observed in rats or rabbits for a variety of tests. From this study a lowest-observed adverse-effect-level (LOAEL) of 382 ppm and a NOAEL of 99 ppm for rats for changes in liver

weight were identified. For mice an LOAEL of 782 ppm and an NOAEL of 382 ppm for organ weight changes were identified. For rabbits, an LOAEL of 1,610 ppm and an NOAEL of 782 ppm for body weight changes were determined.

F344/N rats and B6C3F1 mice (10/sex/group) were exposed to 0, 100, 250, 500, 750 or 1,000 ppm ethylbenzene for six hours/day, five days/week for 13 weeks (NTP, 1992). Among exposed rats, absolute and relative liver, lung and kidney weights were increased, with the increase in absolute and relative liver weights observed among male rats in the 250 ppm dose group and higher, and among female rats in the 500 ppm dose group and higher. Absolute and relative kidney weights were significantly increased among male and female rats in the 500, 750 and 1,000 ppm dose groups (with the exception of male rats in the 500 ppm dose group where this effect was not significant). Regeneration of the kidney tubules was observed in male rats in all dose groups with increased severity with dose. Serum alkaline phosphatase was significantly increased among male and female rats at doses of 500 ppm and higher. Enlarged lymph nodes (bronchial and mediastinal) and lung inflammation observed in exposed groups was determined by the investigators to be an infection rather than an exposure-related effect, although further evaluation of this observation was recommended. Among male and female mice, absolute and relative liver weights were increased in the two highest dose groups. Among female mice in the high-dose group, relative kidney weights were significantly increased. NTP concluded that there was only minimal evidence for the toxicity of ethylbenzene in rats and mice at the doses tested. In this study, the LOAEL was considered to be 250 ppm ethylbenzene for liver weight changes and increased renal tubular regeneration in rats; the study NOAEL was 100 ppm.

Several species were repeatedly exposed to ethylbenzene by inhalation (Wolf *et al.*, 1956). Among rats (10 to 25/group) exposed to 400, 600, 1,250 or 2,200 ppm ethylbenzene for seven hours/day, five days/week for 186 to 214 days, all groups exhibited slightly increased liver and kidney weights. Rats in the two highest dose groups also exhibited growth depression as well as liver and kidney histopathology characterized as cloudy swelling. Among guinea pigs (5 to 10 per group) similarly exposed to 400, 600 or 1,250 ppm ethylbenzene, animals in the highest dose group exhibited growth depression and those in the mid-dose group exhibited a slight increase in liver weight. Among rabbits (one to two/group) similarly exposed to 400, 600 or 1,250 ppm ethylbenzene, testicular histopathology (degeneration of the germinal epithelium) was observed in the mid-dose group. Among Rhesus monkeys exposed to 400 ppm (two females) or 600 ppm (one male) ethylbenzene, the male exhibited testicular histopathology as well as slightly increased liver weight. An LOAEL of 400 ppm ethylbenzene was established in rats for changes in liver and kidney weights. In guinea pigs an LOAEL of 1,250 ppm was established, with an NOAEL of 600 ppm. The utility of this study is somewhat limited by scant reporting of the experimental findings and, with rabbits and monkeys, a limited number of experimental animals. The nature of the control group for each of the experiments was also unclear.

Female rats (10/group) were also administered ethylbenzene 0, 13.6, 136, 408 or 608 mg/kg-day orally by intubation for six months, five days/week (Wolf *et al.*, 1956). Effects observed in the two highest dose groups included cloudy swelling of liver cells and the renal tubular epithelium with increased liver and kidney weight. The LOAEL for this study is 408 mg/kg-day and the NOAEL is 136 mg/kg-day.

Wistar rats (18/sex/group) were exposed by inhalation to 0 or 100 ppm ethylbenzene for six hours/day, five days/week for 12 weeks (Clark, 1983). No statistically significant adverse effects

were observed among the exposed animals. An NOAEL of 100 ppm ethylbenzene was identified from this study.

In a study of liver effects, male Wistar rats (five/group) were exposed by inhalation to 0, 50, 300 or 600 ppm ethylbenzene for six hours/day, five days/week for 2, 5, 9 or 16 weeks (Elovaara *et al.*, 1985). Proliferation of the smooth endoplasmic reticulum and degranulation of the rough endoplasmic reticulum was evident at two to nine weeks. A number of serum enzyme activities were increased after 16 weeks including NADPH-cytochrome reductase and UDPG-transferase (300 and 600 ppm), and aminopyrine N-demethylase and 7-ethoxycoumarin-O-deethylase (all dose groups).

Six-month exposure of rabbits to 400 mg/kg ethylbenzene (presumably oral) was reported to produce segmentation of the nuclei of blood leukocytes (Pokkrovskii and Volchkova, 1968). Seven-months exposure of rabbits to 100 or 1,000 mg ethylbenzene/m^3 was reported to lead to hematological effects (white blood cell count changes), dystrophia of the liver and kidney and muscle chronaxia (Ivanov, 1962; Ivanov, 1964).

Noncarcinogenic Chronic Effects

Fisher 344/N rats and B6C3F1 mice (50/sex/group) were exposed by inhalation to 0, 75, 250 or 750 ppm ethylbenzene for two years (six hours/day, five days/week) (NTP, 1996). Survival was significantly decreased among high-dose male rats. Among male and female rats in the high-dose group the severity of nephropathy was increased over control animals. It was speculated by the investigators that the reduced survival rate observed among male rats in the high-dose group was caused in part by the exacerbation of nephrotoxicity, which is frequently observed among aging male rats. Cystic degeneration of the liver was significantly increased in the high-dose group. Increased incidences of edema, congestion and hemorrhage of the lungs and hemorrhage of the renal lymph nodes were slightly but significantly increased among animals in the high-dose group, although it was speculated that these were indirect effects among moribund animals. Prostate gland inflammation, characterized as infiltration of mononuclear cells into the glandular acini and interstitium, were also increased in all groups of male rats relative to controls. Hypercellularity of the bone marrow (increased erythroid and myeloid precursors) was increased in animals in both high- and low-dose groups. A clear dose-response was not evident for either the prostate or bone marrow effects. An LOAEL for renal and liver effects was established to be 750 ppm ethylbenzene for rats, with an NOAEL of 250 ppm.

Among male mice, hepatotoxicity was evident and included significantly increased observations of liver hypertrophy (high-dose), necrosis (high-dose) and alterations of hepatic syncytia (mid- and high-dose). Eosinophilic liver foci were significantly increased among female mice in the high-dose group. For B6C3F1 mice, an LOAEL of 250 ppm ethylbenzene is established for hepatotoxicity in males, with a corresponding NOAEL of 75 ppm.

Developmental and Reproductive Toxicity

Female CFY rats (17 to 20/group) were exposed to 0, 600, 1,200 or 2,400 mg/m^3 ethylbenzene (0, 136, 271 and 543 ppm, respectively) continuously from days 7 to 15 of pregnancy (Ungváry and Tátrai, 1985). The authors reported "moderate and dose-dependent" maternal toxicity in rats, although the nature of the toxicity was not presented. Skeletal retardation was also reported among the exposed rats, and the incidences of extra ribs, anomalies of the uropoietic apparatus and

skeletal malformations were increased in the high-dose group. Post-implantation loss was also increased among exposed rats. The LOAEL for rats in this study is 543 ppm ethylbenzene, with an NOAEL of 271 ppm. Female CFLP mice and New Zealand rabbits were exposed to 0, 500 or 1,000 mg/m^3 ethylbenzene (0, 113 and 226 ppm, respectively) continuously from days 6 to 20 of pregnancy. Among mice, an increase in the incidence of skeletal retardation and weight retarded fetuses was observed. Mice also showed an increase in the incidence of anomalies to the uropoietic apparatus. Among rabbits, mild maternal toxicity (decreased weight gain) and increased loss to abortion were observed in the high-dose group. Weight retardation was observed among fetuses in the low-dose group. No teratogenic effects were observed.

Female Wistar rats (78 to 107/group) and New Zealand white rabbits (29 to 30/group) were exposed by inhalation for six to seven hours/day to 0, 100 or 1,000 ppm ethylbenzene during gestational days 1 to 19 (rats) or 1 to 24 (rabbits) (Andrew *et al.*, 1981; also reported in Hardin *et al.*, 1981). There was no evidence of embryotoxicity, fetotoxicity or teratogenicity among rabbits, nor was there evidence of maternal toxicity. A significant decrease in the number of live rabbit kits/litter was observed in both exposed groups, although there was some question regarding the reporting of the data in the low-dose group. Among rat dams in the high-dose group, evidence of toxicity included increases in the absolute and relative weight of the liver, kidney and the spleen. Increased incidences of fetuses with supernumerary and rudimentary ribs (high-dose) and extra ribs (high- and low-dose) were also observed. In this study, the LOAEL was considered to be 1,000 ppm ethylbenzene for developmental effects in rabbits and rats and maternal toxicity in rat dams. The corresponding NOAEL is 100 ppm.

In a supplemental experiment, female rats were exposed to 0, 100 or 1,000 ppm ethylbenzene, six to seven hours/day, for three weeks prior to mating with exposure continuing into pregnancy (Andrew *et al.*, 1981). Among rat dams in the high-dose group, absolute and relative liver and spleen weights were increased and relative kidney weight was increased significantly. Among the fetuses in the high-dose group, the incidence of extra ribs was significantly increased. The LOAEL and NOAEL for this study are 1,000 and 100 ppm ethylbenzene, respectively.

Genetic Toxicity

Five strains of *Salmonella* showed no evidence of mutagenicity from exposure to ethylbenzene either with or without metabolic activation, nor was there evidence in two *Escherichia coli* strains or in a *Saccharomyces cerevisiae* gene conversion assay (Nestmann *et al.*, 1980; Dean *et al.*, 1985; Zeiger *et al.*, 1992; Florin *et al.*, 1980). The lack of mutagenicity of ethylbenzene to *Salmonella* has been confirmed in testing by NTP; additionally no indications of increased sister-chromatid exchange or chromosomal aberrations were observed in Chinese hamster ovary cells (NTP, 1996). Ethylbenzene induced a mutagenic response in a mouse lymphoma assay without metabolic activation, but only at a dose which resulted in cytotoxicity (McGregor *et al.*, 1988; NTP, 1996). In addition, a 13-week exposure of mice by inhalation to ethylbenzene concentrations of 500, 750 or 1,000 ppm did not result in an increase in the frequency of micronucleated erythrocytes (MacGregor *et al.*, 1990).

Carcinogenicity

Fisher 344/N rats and B6C3F1 mice (50/sex/group) were exposed by inhalation to 0, 75, 250 or 750 ppm ethylbenzene for two years (six hours/day, five days/week) (NTP, 1996). Survival rate and mean body weight were lower among male rats in the high-dose group relative to control animals. The incidences of renal tumors among male rats are summarized in Tables 1 and 2. In addition, the incidences of interstitial cell adenoma and renal tubule hyperplasia were significantly increased among male rats in the high-dose group.

Table 1. Kidney Tumors in Male Rats Exposed to Ethylbenzene (Single Sections) (NTP, 1996)

Tumor Type	Exposure Concentration (ppm)			
	0	75	250	750
Tubular cell adenoma	0/50	3/50	2/50	4/50[*]
Tubular cell carcinoma	0/50	0/50	1/50	3/50
Tubular cell tumors (combined)	0/50	3/50	3/50	7/50[*]

[*]Significantly increased incidence.

Table 2 presents the results of a further evaluation of renal tumors in male and female rats using the results of the single sections combined with those of step sections. In addition to these observations, the incidences of renal tubule hyperplasia were also increased significantly among both male and female rats in the high-dose group. NTP reported no evidence of hyaline droplet formation in the kidneys in this study (or in the earlier 13-week study), indicating that nephropathy due to the accumulation of $\alpha_{2\mu}$-globulin is unlikely to be the mechanism of kidney toxicity with ethylbenzene.

Table 2. Kidney Tumors in Rats Exposed to Ethylbenzene (Single and Step sections) (NTP, 1996)

Tumor Type	Exposure Concentration (ppm)							
	0		75		250		750	
	Male	Female	Male	Female	Male	Female	Male	Female
Tubular cell adenoma	3/50	0/50	5/50	0/50	7/50	1/50	20/50[*]	8/49[*]
Tubular cell carcinoma	0/50		0/50		1/50		3/50	
Tubular cell tumors (combined)	3/50		5/50		8/50		21/50[*]	

[*]Significantly increased incidence.

The incidence of testicular adenomas (interstitial and bilateral) was also increased among high-dose male rats (36/50, control; 33/50, low-dose; 40/50, mid-dose; 44/50, high-dose; $p < 0.05$ by Fisher's Exact Test).

The incidences of several tumor types were increased significantly among the B6C3F1 mice (Table 3). Among male mice in the high-dose group, the incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined) were increased over controls. The incidences among exposed groups, however, was within the range of historical controls (10 to 42% for combined tumors). Among female mice in the high-dose group, the incidences of combined hepatocellular adenoma or carcinoma and hepatocellular adenoma alone were significantly increased over control animals, although again the incidence among exposed animals was within the range of historical controls (3 to 54% for combined tumors).

Table 3. Tumors in B6C3F1 Mice Exposed to Ethylbenzene (NTP, 1996)

Tumor Type	Exposure Concentration (ppm)							
	0		75		250		750	
	Male	Female	Male	Female	Male	Female	Male	Female
Alveolar or bronchiolar adenoma	5/50		9/50		10/50		16/50[*]	
Alveolar or bronchiolar adenoma + carcinoma	7/50		10/50		15/50		19/50[*]	
Hepatocellular adenoma		6/50		9/50		12/50		16/50[*]
Hepatocellular adenoma + carcinoma		13/50		12/50		15/50		25/50[*]

[*]Significantly increased incidence ($p < 0.05$).

Thyroid gland follicular cell hyperplasia incidences were increased among male and female mice in the high dose group. Among female mice in the high- and mid-dose groups, the incidences of hyperplasia of the pituitary gland *pars distalis* was significantly increased (10/48, control; 12/49, low-dose; 23/47, mid-dose; 22/49, high-dose; $p < 0.05$ by Fisher's Exact Test).

In another study of the carcinogenicity of ethylbenzene, Sprague-Dawley rats were administered 500 mg/kg ethylbenzene by oral gavage for four or five days/week for 104 weeks (Maltoni *et al.*, 1985). An increase in the incidence of total malignant neoplasms was reported for both male and female rats. Tumor types were not specified in the study.

Weight-of-Evidence for Carcinogenicity

Only two studies have been conducted examining the carcinogenicity of ethylbenzene in experimental animals (NTP, 1996; Maltoni *et al.*, 1985). The study by Maltoni *et al.* (1985) was conducted with only a single dose of ethylbenzene and details of the results were not presented (total tumors). Therefore, the usefulness of the study is limited for the evaluation of carcinogenicity, although a significant increase in total neoplasms was reported.

The chronic bioassay conducted by NTP demonstrated the induction of several tumor types in rats and mice exposed to ethylbenzene by inhalation (NTP, 1996). The study appears to be well-conducted and appropriately designed for the evaluation of the carcinogenicity of the test compound in experimental animals, given the available information on the toxicity of ethylbenzene. Dose selection was made based upon the results of previous subchronic studies and proved to be adequately close to the maximum tolerated dose (MTD) as demonstrated by the limited increase in mortality observed at the end of the two-year study. Significantly increased incidences of tumors included combined renal tubule adenomas and carcinomas in male rats, testicular adenomas in male rats, renal tubule adenomas in female rats, combined alveolar and bronchiolar adenomas and carcinomas in male mice and combined hepatocellular adenomas and carcinomas in female mice. In the case of lung tumors in male mice and liver tumors in female mice, the tumor incidences were within the range of incidences for historical controls.

The most clear evidence of carcinogenicity was demonstrated by the development of renal tubule tumors in male rats. The appearance of renal tubule tumors in male rats raises the possibility that the tumors were induced by a mechanism involving the hyperplastic response mediated by the binding of the test compound to $\alpha_{2\mu}$-globulin leading to accumulation which results in nephrotoxicity and a hyperplastic response, a mechanism which has been hypothesized for certain strains of male rats (including Fisher 344/N) but determined not to be relevant to humans for the purposes of risk assessment because of the absence of significant amounts of $\alpha_{2\mu}$-globulin in humans (U.S. EPA, 1991d). With regard to the involvement of this mechanism in the evaluation of the carcinogenicity of ethylbenzene, there are several observations to consider:

1) The current NTP study as well as the 13-week study which preceded it (NTP, 1992) demonstrated no evidence of the formation of hyaline droplets in the kidneys, a hallmark of the accumulation of $\alpha_{2\mu}$-globulin and a requirement for the induction of nephropathy by this proposed mechanism.

2) There was evidence of renal effects in female rats including a significantly increased incidence of renal tubule adenomas and hyperplasia in the high-dose group as well as an increased severity of nephropathy with increasing dose.

3) Since the $\alpha_{2\mu}$-globulin-mediated effect is specific to male rats, this observation provides evidence that for rats exposed to ethylbenzene, another mechanism leading to renal lesions is likely to be mediating toxicity.

For these reasons, the renal lesions observed in the study were considered relevant to human health risk assessment and the calculation of a PHG for ethylbenzene in drinking water.

While the NTP (1996) study overall provides some evidence for the carcinogenicity of ethylbenzene in experimental animals, there are several issues which need to be considered before a complete appraisal of the carcinogenic effect can be made and its relevance to humans established. These concerns include the contribution of chronic injury or cytotoxicity to tumor development, the appropriateness of using historical controls in decreasing the weight-of-evidence for significantly elevated tumor incidences, and the biological relevance of increased hepatocellular tumors in female B6C3F1 mice.

Toxicological Effects in Humans

Acute Effects

An early report on the toxicity of ethylbenzene in air demonstrated intolerable irritation of the eyes and nose at 5,000 ppm, tearing, dizziness and nose irritation at 2,000 ppm and eye irritation at 1,000 ppm ethylbenzene (Yant *et al.*, 1930). CNS depression occurs at 2,000 ppm ethylbenzene. A later report showed a threshold of 200 ppm ethylbenzene for irritation of the eyes and mucous membranes (Gerarde, 1959). Increasing the exposure level to 2,000 ppm ethylbenzene (six minutes) resulted in dizziness and more severe irritation of the eyes and nose. Eighteen human subjects (male) exposed to 100 ppm ethylbenzene for up to eight hours reported mild irritation of the eyes and respiratory system plus tiredness, insomnia and headache (Bardodej and Bardodejova, 1970). Skin contact may result in erythema and inflammation (Lewis, 1992).

Subchronic Effects

Prolonged inhalation exposure to levels as low as 23 to 230 ppm ethylbenzene may result in leukopenia, lymphocytosis, neurofunctional disorder and hepatitis, while lower levels of exposure (2.3 ppm) may result in inflammation of the mucosa of the upper respiratory tract (HSDB, 1997; citing ILO, 1983).

In an epidemiological study of 200 workers involved in the production of ethylbenzene, no statistically significant differences in hematological parameters (including red and white blood cell counts, platelet counts) or liver function tests (including bilirubin, LDH and SAP levels) were observed between exposed and non-exposed subjects (Bardodej and Cirek, 1988). Exposure levels were not quantitated, but mean duration of exposure was 12.2 years.

Developmental and Reproductive Toxicity

No data have been located in the scientific literature regarding the developmental and reproductive toxicity of ethylbenzene to humans.

Genetic Toxicity

Ethylbenzene slightly increased the incidence of sister chromatid exchange in human whole blood lymphocyte cultures without metabolic activation (Norppa and Vainio, 1983).

Carcinogenicity

No human data have been located in the scientific literature as supporting evidence for the carcinogenicity of ethylbenzene.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Numerous studies have identified adverse noncarcinogenic effects resulting from exposure to ethylbenzene. However, no suitable data are available from epidemiological studies of human populations or case reports of human exposures for conducting a dose-response analysis. The few case reports which are available, as well as the limited number of chamber studies, are limited by inadequate estimation of exposure levels or by insufficient exposure duration for establishing effects which may result from long-term exposure.

Several studies conducted with experimental animals have established minimum levels of exposure associated with adverse toxicological effects (LOAELs) as well as levels without apparent effect (NOAELs). The only chronic exposure study examining toxicity in experimental animals which included noncarcinogenic endpoints is the NTP (1996) inhalation bioassay. High- and mid-dose mice showed evidence of liver toxicity. The LOAEL established from this study is 250 ppm (164 mg/kg-day; see below) with an NOAEL of 75 ppm (49.3 mg-kg/day). In the analysis of a dose-response for the noncarcinogenic effects of ethylbenzene, the inhalation dose rate was converted to an equivalent dose rate in units of mg/kg-day. For rats, this unit conversion was based on 4.42 mg/m^3 per ppm ethylbenzene (at 20°C), a rat breathing rate of 0.26 m^3/day (adjusted for experimental conditions of six hours/day, five days/week) and a rat body weight of 0.35 kg. A reasonable estimate of the fractional absorption of ethylbenzene from inhalation exposure of 50% was used based upon experimental findings in both animals and humans (see "Metabolism and Excretion" above). For mice, the conversion was based on the same defaults with the exception of a mouse breathing rate of 0.05 m^3/day and a mouse mean body weight of 0.03 kg. Therefore, the inhalation doses of 75, 250 and 750 ppm ethylbenzene were converted to daily dose rates of 22.0, 73.3 and 220 mg/kg-day, respectively, for rats and 49.3, 164 and 493 mg/kg-day for mice.

Only two subchronic studies of the toxicity of ethylbenzene by the oral route are available. One is a six-month study with rabbits administered (presumably orally) a single dose level of 400 mg/kg-day showing hematological effects (Pokrovskii and Volchkova, 1968). The second (Wolf *et al.*, 1956) provided evidence for liver and kidney effects in rats at doses (administered by intubation) as low as 408 mg/kg-day (the LOAEL), with no effects observed at the next lowest dose of 136 mg/kg-day (the NOAEL).

Subchronic inhalation studies have demonstrated a number of effects for ethylbenzene exposure in experimental animals. Cragg *et al.*(1989) observed adverse effects (organ weight changes) in rats exposed to ethylbenzene levels as low as 382 ppm (LOAEL), with no effects observed at 99 ppm (NOAEL). The NTP (1992) studies showed organ weight changes among rats in four dose groups exposed to 250 ppm ethylbenzene (LOAEL) and higher with no effects observed at 100 ppm (NOAEL). Inhalation studies by Wolf *et al.* (1956) showed organ weight effects among rats exposed to 400 ppm ethylbenzene (LOAEL), the lowest dose tested. Clark (1983) observed no

adverse effects in rats exposed to 100 ppm ethylbenzene for 12 weeks. Metabolic enzyme and mild subcellular changes to the liver were observed in the 16-week study by Elovaara *et al.* (1985) at exposure levels as low as 50 ppm ethylbenzene, however it is not clear that the nature of these changes was adverse.

From animal developmental and reproductive toxicity studies, evidence of maternal toxicity was observed in inhalation exposures at 1,000 ppm ethylbenzene (Andrew *et al.*, 1981) with no adverse effects observed at 100 ppm (NOAEL). In the study by Ungváry and Tátrai (1981), the LOAEL was taken to be 543 ppm ethylbenzene for developmental effects in the offspring of exposed rats, with an NOAEL of 271 ppm. Among mice in the same study low-dose (113 ppm) offspring showed weight retardation (LOAEL).

The NOAEL in mice derived from the chronic inhalation studies (NTP, 1996) was selected as the most sensitive endpoint for noncarcinogenic effects despite some uncertainty regarding the route-to-route conversion. Inhalation studies have provided the most consistent evaluation of the toxicity of ethylbenzene, also evidenced by the fairly consistent dose level (when accounting for the exposure regimen) which is without adverse effect in experimental animals in the subchronic exposure studies. There is also the question as to whether the endpoints observed are route-specific. However, the evidence from both inhalation and oral studies suggests there are common endpoints of toxicity, including liver and kidney toxicity. Furthermore, broad toxicity was observed by both routes. While several subchronic studies provided comparable NOAELs, the NTP (1996) chronic exposure study is the most suitable evaluation of noncarcinogenic endpoints for purposes of developing a PHG for ethylbenzene in drinking water because of the chronic nature of the exposure. The value from this study (and the route-converted dose of 49.3 mg/kg-day) has been selected as the overall NOAEL for adverse noncarcinogenic effects from exposure to ethylbenzene in experimental animals.

Carcinogenic Effects

A dose-response evaluation for the carcinogenic effects of ethylbenzene is not presented because of the preliminary nature of the findings of the NTP (1996) study. However, because of the potential for a carcinogenic effect from ethylbenzene exposure, an additional uncertainty factor (UF) of 10-fold has been included in the calculation of the PHG level (see below).

CALCULATION OF PHG

A public health-protective concentration (C, in mg/L) for ethylbenzene in drinking water can be calculated based on the general equation for noncarcinogenic endpoints:

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

where,

NOAEL	=	No-observed-adverse-effect-level (49 mg/kg-day)
BW	=	Adult male body weight (70 kg)
RSC	=	Relative source contribution of 20% (0.2)
UF	=	Uncertainty factor of 1,000 (see text)
L/day	=	Volume of water consumed daily by an adult (2 L/day).

In the case of ethylbenzene, the experimental NOAEL for the principle study (NTP, 1996) was determined to be 49 mg/kg-day. The adult human body weight default is 70 kg for a male. An RSC of 20% was used in the calculation in the absence of more specific information on exposures to other sources of ethylbenzene exposure in addition to drinking water. A cumulative uncertainty factor of 1,000 has been applied which incorporates uncertainty contributions for inter-species extrapolation (10) and potentially sensitive human subpopulations (10), plus an additional factor of 10 for uncertainty from potential severe endpoints (carcinogenicity). U.S. EPA has applied a similar safety factor in establishing a long-term health advisory for drinking water when preliminary evidence has suggested a carcinogenic effect from a chemical (Anonymous, 1988). The adult human water consumption default value is 2 L/day.

Therefore,

$$C = \frac{49 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{1{,}000 \times 2 \text{ L/day}}$$

$$= 0.343 \text{ mg/L} = 0.3 \text{ mg/L (rounded)} = 300 \text{ ppb.}$$

Based on this calculation, OEHHA proposes a PHG of 0.3 mg/L (300 ppb) for ethylbenzene in drinking water.

RISK CHARACTERIZATION

There are a number of areas of uncertainty in regard to the development of the PHG for ethylbenzene in drinking water including route-to-route dose extrapolation (see discussion above), as well as the general toxicological concerns regarding extrapolation to humans of data from experimental animals which are acknowledged in the use of uncertainty factors. In addition, for volatile chemicals such as ethylbenzene exposures through food are unlikely, so the relative source contribution from water could perhaps be set higher than the default value of 0.2. However, net exposures to ethylbenzene in water could also be higher than estimated using the default 2 L/day of water consumption because of inhalation of the solvent vapors during showering and other household activities. The magnitude of these factors has not been estimated for ethylbenzene. It has been assumed that the factors would tend to offset each other (e.g., RSC = 40%, drinking water equivalent = 4 L/day), so the defaults have been retained for this calculation.

Several subpopulations in the general population who may be especially sensitive to the noncarcinogenic effects of ethylbenzene have been identified (HSDB, 1997). They include: individuals whose pulmonary function may be impaired (obstructive airway disease) and individuals with existing skin, liver, kidney, nervous system, blood and hematopoietic, ovulation and or menstrual disorders. The pulmonary and skin disorders are relevant for inhalation and dermal exposures, while the other disorders may be relevant for effects from drinking water exposure. No special sensitivity of infants and children has been noted for ethylbenzene. It is considered that the UF of 10-fold to account for human variability plus another 10-fold for uncertainty about a possible severe endpoint (cancer) should be adequate to protect potentially sensitive subpopulations. No evidence of synergy with other chemicals in the toxicity of ethylbenzene was found in the literature.

OTHER STANDARDS AND REGULATORY LEVELS

U.S. EPA has established a Maximum Contaminant Level Goal (MCLG) and a Maximum Contaminant Level (MCL) of 0.7 mg/L for ethylbenzene which U.S. EPA concluded would protect against the potential health problems identified in its report and is "the lowest level to which water systems can reasonably be required to remove this contaminant should it occur in drinking water" (U.S. EPA, 1991b; U.S. EPA, 1991c). This value was based on histopathological changes observed in a six-month rat study yielding a Drinking Water Equivalent Level (DWEL) of 3.4 mg/L assuming a drinking water contribution of 20%. U.S. EPA stated that the DWEL for ethylbenzene is "a lifetime exposure concentration protective of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from a drinking water source." (U.S. EPA, 1996). The availability of new data regarding the chronic toxicity of ethylbenzene (NTP, 1996) since U.S. EPA's evaluation is the source of the departure from this value with OEHHA's proposed PHG. The current California MCL is also 0.7 mg/L (700 ppb).

U.S. EPA also established an ambient water quality criterion of 1.4 mg/L for ethylbenzene ingested through water and contaminated aquatic organisms and an ambient water quality criterion of 3.28 mg/L for ethylbenzene ingested through contaminated aquatic organisms alone (U.S. EPA, 1980).

The Occupational Safety and Health Administration (OSHA) established a workplace exposure standard of 100 ppm ethylbenzene in air for an eight-hour workday. The American Congress of Governmental Industrial Hygienists (ACGIH) has established a threshold limit value of 100 ppm and a short-term exposure limit of 125 ppm in air.

Various states have set guidelines for drinking water concentrations and acceptable ambient air concentrations. These are shown in Tables 4 and 5 (HSDB, 1997; ATSDR, 1990).

Table 4. State Drinking Water Guidelines

State	Drinking Water Guideline
Arizona	680 ppb
California	680 ppb
Illinois	1 ppb
Kansas	680 ppb
Maine	700 ppb
Minnesota	680 ppb
New Mexico	750 ppb
Rhode Island	680 ppb
Vermont	1,400 ppb
Wisconsin	700 ppb

Table 5. State Ambient Air Guidelines

State	Ambient Air Guideline
Connecticut	8,700 µg/m^3 (8 hours)
Massachusetts	118 µg/m^3 (24 hours)
Nevada	10,357µg/m^3 (8 hours)
New York	1,450 µg/m^3 (1 year)
North Dakota	4,350 µg/m^3 (8 hours)
South Carolina	4,350 µg/m^3 (24 hours)
Virginia	7,250 µg/m^3 (24 hours)

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