Public Health Goal for
XYLENE
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 1.8 ppm is developed for xylene(s) in drinking water. The State of California's Maximum Contaminant Level (MCL) for xylene in drinking water is 1.75 ppm based on minimal effects in a chronic rat study. The U.S. Environmental Protection Agency's (U.S. EPA's) MCL is 10 ppm based on the same chronic rat study. Xylene does not appear to be carcinogenic in animals or humans. The calculated PHG considers noncarcinogenic effects in both animals and humans and is based on subjective reports of neurotoxic effects in chronic exposures to xylene in humans. The lowest-observed-adverse-effect level (LOAEL) from this study was divided by a factor of 30 [three for extrapolation from a LOAEL to a no-observed-adverse-effect level (NOAEL) and 10 for potential variations in sensitivity among humans] to calculate a public health-protective level. This value was further divided by two to account for extra exposure by the inhalation route to xylene in the household water supply, and corrected for an assumed relative source contribution from drinking water of 40%. Based on these considerations and assumptions, OEHHA calculates a PHG of 1.8 mg/L (1.8 ppm) for individual xylene isomers or the sum of xylene isomers in drinking water.

INTRODUCTION

The purpose of this document is to develop a PHG for xylene in drinking water. Xylene is a widely-used solvent found in petroleum and coal tar. It consists of a benzene ring with two methyl groups attached, which can vary in position to produce three closely-related forms. These forms are known as xylene isomers, or simply xylenes, but the generic term xylene is commonly used to refer to the mixture of isomers (as in this document). More detail on its chemistry is found in the following section.

Although xylene is a natural chemical, it is not generally found at levels of toxicological and regulatory concern in the environment, in air, water or soil. This is due to its relatively low toxicity, its ability to be metabolized (broken down to simpler components) by both sunlight and bacteria and its lack of bioaccumulation in animals. Therefore, any significant exposures to xylene are the result of its production and use as a solvent, a chemical intermediate or as a fuel component.

Xylene is one of the most widely used chemicals, with production rates in the United States (U.S.) of around 10 billion pounds per year (ATSDR, 1995), including mixed xylenes and the individual isomers. It is used in paint thinners, varnishes, as a rubber solvent in the tire industry, in printing and paper manufacturing, as a solvent in the plastic industry and as a component of gasoline and fuel oils. The individual isomers are used in the manufacture of certain polymers (plastics). This widespread use results in great opportunities for both occupational and residential exposures. Synthesis, transport, storage and use of the large quantities of xylene also result in many opportunities for spills, leaks and process losses (such as in the drying of paints) (ATSDR, 1995).

Because of the ready volatilization of xylene and its low solubility in water, released xylene is expected to enter the atmosphere, where it is dispersed and then destroyed in sunlight. Xylene levels in air are commonly in the range of 10 to 40 parts per billion (ppb) in the U.S. (IARC, 1989), with the lower end of the range found in rural areas and the higher levels in urban settings closer to the major sources. Background concentrations of xylene of about 2 to 8 µg/L have been found in surface water and drinking water (Merian and Zander, 1982). Much higher levels have

been found in soil as a result of spills or leaks from fuel storage tanks. This can result in a significant threat to drinking water supplies and it is to protect against this problem that regulatory levels for drinking water have been developed.

The U.S. Environmental Protection Agency (U.S. EPA) derived a Maximum Contaminant Level (MCL) for xylenes in drinking water of 0.44 parts per million (ppm) in 1981 (U.S. EPA, 1981). The State of California recommended an action level for xylene isomers or mixed xylenes of 0.62 ppm (FSTRAC, 1988), and then proposed an MCL of 1.75 ppm (DHS, 1987) which was promulgated in 1989. U.S. EPA increased its MCL for xylene to 10 ppm (U.S. EPA, 1991) based on the chronic toxicity information in the 1986 National Toxicology Program (NTP) studies in rats and mice (NTP, 1986). The Agency for Toxic Substances and Disease Registry (ATSDR) (1995) recommended minimal risk levels for exposures to xylene or its individual isomers which would provide significantly lower equivalent exposures than in U.S. EPA's drinking water standard, based on self-reported effects in humans (Uchida *et al.*, 1993). These various studies and recommendations are discussed in more detail below for deriving a PHG.

CHEMICAL PROFILE

Xylene is found in small proportions in petroleum and coal tar and also can be formed by the catalytic processes used in a petroleum refinery. The molecule consists of a benzene ring with two attached methyl groups. Because these methyl groups can be in different relative positions on the six-carbon benzene ring, three forms of xylene, called isomers, are possible as shown in Figure 1. The three isomers, ortho-, meta- and para-xylene (o-, m- and p-xylene), have similar properties and are thus isolated together from their mixed hydrocarbon sources.

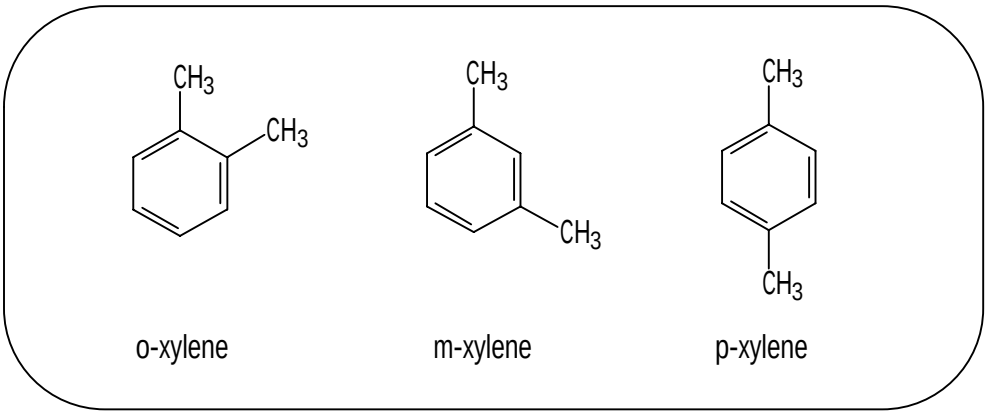

Figure 1. The Three Isomers of Xylene

The molecular weight of xylene is 106.2 grams/mole. The boiling points of the three isomers are 144 ^{o}C, 139.3 ^{o}C and 137 to 138 ^{o}C for the o-, m- and p-isomers, respectively. They are commonly found in a technical grade xylene mixture in the proportions of 45 to 55% m-xylene and about 20% of each of the o- and p-isomers, with the remainder being ethylbenzene. The xylene isomers have water solubilities of about 0.02%. The vapor pressure at standard temperature and pressure of o-xylene is about 7 mm Hg and its specific gravity is 0.88. For the other two isomers, the vapor pressure is about 9 mm Hg and the specific gravity about 0.86 (NIOSH, 1994). Sax and Lewis (1989) gives slightly lower vapor pressure values for all three isomers (5, 6 and 6.5 mm, respectively). The odor thresholds for the three isomers are about 1 ppm in both air and water (ATSDR, 1995).

Other properties important for some estimates of environmental distribution are the octanol/water partition coefficient (log K_{ow} = 3.12 to 3.20 for the various isomers), the organic carbon partition coefficient (log K_{oc} = 2.1 to 2.3 for the isomers) and the Henry's law constant (0.00519, 0.00766 and 0.00766 atm-m^3/mol for the o-, m- and p-isomers, respectively) (ATSDR, 1995, Table 3.2.).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Xylene can be introduced into air from forest fires or from natural petroleum seeps, but most atmospheric xylene is a product of human activities. Therefore, concentrations in air in urban areas, especially near industrial sites, tend to be several times the concentrations in rural areas. According to U.S. EPA's Toxic Release Inventory (TRI), 108.6 million pounds of mixed xylenes were released into the environment in 1994 from reporting industrial facilities. Of this amount, 23% was released into the air from fugitive (non-point source) emissions and 77% from stack or point emissions into the air; releases to land and water were less than 1% of the total.

As one of the 17 priority chemicals targeted for release reduction by U.S. EPA, industrial releases of xylene have been decreasing from many facilities. Of the 3,346 TRI forms reporting xylene releases in 1994, 1,211 (36.2%) reported a decrease compared to the previous year (U.S. EPA, 1997a).

Current concentrations of xylene in air are not available, but concentrations in air of up to about 40 ppb have commonly been found in urban areas of the U.S. (IARC, 1989). Rural areas are generally much lower. Concentrations of xylene in surface water and drinking water have been reported to be about 2 to 8 µg/L (Merian and Zander, 1982), but because the xylene usage and release patterns have changed greatly since these measurements, these values should not be considered dependable.

Concentrations of xylene in soil may be quite high in the vicinity of spills or leaking fuel storage tanks. Xylene has also been detected at a large proportion of hazardous waste disposal sites (although little land disposal of xylene wastes is presently occurring). Rapid transfer of xylene to air is expected from surface soils because of its high volatility and low soil binding. Therefore, soil is not a significant direct exposure medium for xylene. Xylene is relatively stable in soil, so it can persist for many years in deeper soil pockets. The low solubility of xylene in water (approximately 0.02%) means that it is not leached rapidly away into ground water. With a high-volume spill, xylene can be present in a separate organic solvent phase, floating on the ground water.

Release of xylene-containing aqueous wastes into surface waters or contamination of surface water with xylene from spills should result in rapid evaporation of xylene from the water. The volatilization half-life of 5.6 hours (MacKay and Leinonen, 1975) is much shorter than the biodegradation rate, with an estimated half-life of about 250 hours (Jori *et al.*, 1986). Nevertheless, because of the very large use of xylene, there is a correspondingly large potential for occasional contamination incidents from xylene spills into surface water or leaching into ground water. This potential has resulted in the present effort to determine a recommended PHG for xylene in drinking water.

Plant food commodities will not become significantly contaminated with xylene by uptake from air because of the high volatility of xylene and relatively low aqueous and lipid solubilities. Similarly, contamination of crops by treatment with xylene-contaminated water should result in low uptake

and relatively rapid loss of xylene from plant tissues. Xylene has not been reported in edible crop tissues; therefore this will not be considered a significant source of xylene exposures. However, aquatic species in xylene-contaminated waters could be expected to retain significant xylene concentrations at equilibrium. Bioaccumulation would be limited by the rapid metabolism of xylene (and exhalation, for air breathers). Bioconcentration factors have been estimated to be in the range of 6 to 105 for various aquatic animal species and about 250 for a green algae (probably higher in the algae because of little or no xylene metabolism) (ATSDR, 1995). Xylene has also been detected in trout and carp taken from rivers not known to be contaminated, at levels of 0.05 ppm for m-xylene and 0.12 ppm for p-xylene (Hiatt, 1983). Bioconcentration factors below 20 are commonly considered indicative of little or no bioaccumulation; factors in the range of 20 to 100 to be equivocal, and less than 1,000 to indicate modest bioaccumulation potential (ATSDR, 1995).

The largest exposure of the general population to xylene would be expected to be from the use of consumer products such as paints, paint thinners, varnishes and fuels. However, the greatly decreased availability and use of oil-based paints and varnishes in California should have lowered the significance of this exposure source. The recent replacement of the octane-increasing mixed aromatics (benzene/toluene/xylene/ethylbenzene) in gasoline with methyl tert-butyl ether presumably decreases population exposure to xylene (as well as other aromatics with potentially additive effects). Occasional daily exposures to xylene may nevertheless still be quite high from use of some spray paints and solvents.

It has been estimated that about one million workers are exposed to xylene each year in the U.S. (NIOSH, 1984). This has resulted in point samples of 400 ppm in air, with eight-hour time-weighted averages (TWA) up to or slightly exceeding 100 ppm (IARC, 1989). The NIOSH TWA for xylene is 100 ppm (NIOSH, 1994). Histology labs, which use xylene for clearing slides and commonly employ women of child-bearing ages, have provided some of the highest xylene exposures. This has been a particularly useful population for epidemiological studies on the potential effects of xylene exposure, because xylene was the major solvent in use (although concurrent exposures to formaldehyde vapors are common). Chemical industry workers who are exposed to elevated levels of xylene are also commonly exposed to other solvents such as toluene or chlorinated hydrocarbons. Other workers who have relatively “pure” xylene exposures are those who use it as a solvent in a production environment, such as in the plastic or textile industry. In paints and varnishes, xylene is usually present as one component of a solvent mixture, commonly at the 5 to 15% level (ATSDR, 1995). Xylene has also been used as a solvent or carrier in many pesticide products. A search through the U.S. EPA pesticide chemical data base for xylene-containing products retrieved only two products for which xylene is a major constituent [Black Leaf (25% methoxychlor), containing 72% xylene, and Royal Brand Beetle Buster (11% azinphos-methyl), containing 84% xylene] (U.S. EPA, 1997b). It is likely that other pesticides also contain xylene, probably in lower concentrations and in mixtures, not called out as a separate ingredient. Significant exposures to xylene through use of these products is likely to be relatively uncommon.

METABOLISM AND PHARMACOKINETICS

Absorption

Xylene is well absorbed orally. Based on some experiments with gavage administration of xylene to animals, 90% absorption of toluene has been estimated (DHS, 1987; ATSDR, 1995). Absorption during inhalation exposure has been estimated at about 60 to 65% for each of the

isomers based on several studies in humans (DHS, 1987; ATSDR, 1995). For dermal exposures, absorption efficiency depends on the exposure conditions. If soil containing xylene were to come into contact with the skin (non-occluded), for example, most of the xylene would be quickly lost by evaporation. We estimate absorption of 1% or less of the xylene in soil under such conditions. With skin occluded, more of the total xylene would be absorbed, depending on soil thickness and contact time. Direct absorption of xylene vapors through the skin from the air has been estimated at 0.1 to 0.2% of inhalation absorption (Riihimaki and Pfaffli, 1978). The rate of dermal absorption of xylene from water is not accurately known, but a K_p (dermal absorption rate coefficient) of 0.08 cm/hour has been estimated (U.S. EPA, 1992a).

Distribution

Considered in the context of organic solvents in general, xylene is relatively soluble in blood. It is rapidly absorbed in the lungs and distributed throughout the body, concentrating in fat. About 90% of the total xylene in blood is bound to plasma proteins; thus the fat to blood ratio will be much less than the octanol/water partition coefficient of 1,200 to 1,600 (calculated from the log K_{ow} of 3.1 to 3.2). Because blood flow to fat is slow, xylene shows biphasic absorption and elimination curves. With short-term inhalation exposures (less than one hour), fat concentrations do not reach equilibrium and elimination of xylene from blood is fairly rapid (i.e., the first, or alpha phase predominates). Within 60 to 90 minutes, most of the xylene is gone. With longer inhalation exposures, more of the total body load is stored in fat and the slower second, or beta phase elimination predominates. Only a small proportion of the dose (about 5%) will be exhaled, with the remainder being metabolized (Toftgard and Gustafsson, 1980).

Metabolism and Excretion

Most of the metabolism of xylene occurs in the liver, with smaller amounts in the lung and kidneys. Methyl hydroxylation was found to be the major mechanism of xylene metabolism in human liver microsomes, forming a methylbenzyl alcohol. This methyl hydroxylation is catalyzed by cytochrome P_{450}-2E1 (Tassaneeyakul *et al*., 1996), which is both a saturable and an inducible metabolic process. The alcohol moiety is oxidized to form methylbenzoic acid (also known as toluic acid) and then largely conjugated with glycine (forming methylhippuric acid) or with glucuronic acid (forming methylbenzyl glucuronide). The conjugates are excreted in the urine. Methylbenzyl mercapturic acid and dimethylphenol and their conjugates are minor metabolites that may also be detected in the urine. Proportions of the various metabolites vary in different species (IARC, 1989).

Assay of methylhippuric acid in the urine is a useful marker of xylene exposure. With occupational inhalation exposures to xylene, methylhippuric acid concentration in the urine at the end of the work shift has been used as a surrogate for total dose, to relate to time-averaged exposures over the workday (Kawai *et al*., 1991; Inoue *et al*., 1993). Analysis of exhaled xylene is less useful for monitoring, because blood and breath levels drop more rapidly after removal from exposure (Pryor *et al*., 1987).

TOXICOLOGY

General Toxicity

The predominant acute effects of xylene in acute exposures are similar to those of other organic solvents (i.e., mild excitation at low dose, followed by sedation and narcosis with higher exposures). The three xylene isomers and the technical-grade mixture have nearly identical effects; some toxicity tests appear to show more potency for one isomer, while another test shows less potency. Xylene has a strong odor and many exposed persons react negatively at concentrations above a few parts per million in air. The odor threshold is about 1 ppm. Human reactions at about 1 to 100 ppm of xylene in air include nausea, headache and eye, nose, throat and lung irritation.

Human exposures for more than a few minutes to concentrations in air of 100 ppm (the NIOSH TWA) or more cause the previously listed symptoms, plus sedation, disorientation and muscular incoordination. Effects in animal studies are similar, including acute excitation followed by sedation, incoordination, altered visual and auditory evoked potentials, muscle spasms and labored breathing. Higher exposures to xylene can cause severe lung irritation, resulting in pulmonary inflammation, edema and hemorrhage (ATSDR, 1995). Death from acute high-concentration inhalation exposures appears to result from respiratory depression rather than lung damage. Liver and kidney damage may also result from single high doses, particularly from oral administration (observed in attempted suicides in humans or gavage administration of the solvent to animals). The four-hour inhalation LC_{50} in rats is about 6,500 ppm and in mice is about 4,000 to 5,000 ppm. The LD_{50} of xylene by gavage (in corn oil) was estimated to be 3.5 g/kg in rats and about 5.5 g/kg in mice (NTP, 1986).

Because of the solubility limit of xylene in water (200 ppm), no acute toxic effects are expected from drinking water contaminated with xylene. There are no studies in animals of the toxicity of xylene in water for this reason. The human taste threshold for xylene in water is about 1 ppm. In general, the acute behavioral effects and effect levels for xylene appear similar in humans to those observed in experimental animals. This is consistent with other observations on related solvents.

Toxicological Effects in Animals

Systemic Toxicity

Acute inhalation causes excitation, sedation and narcosis with increasing concentrations and exposure time, accompanied by irritation of the eyes, nose and lungs. With prolonged or repeated inhalation exposures to xylene in the concentration range of about 50 to 2,000 ppm in air for several hours per day, other effects become significant, including induction of the liver cytochrome P_{450} enzymes which metabolize xylene and other solvents (Pathiratne *et al*., 1986). Liver enzyme induction is additive for the xylene isomers, toluene and ethylbenzene. This effect is associated with increased endoplasmic reticulum in hepatocytes and increased liver weight, without apparent cytotoxicity. Similar effects have been observed in kidney in several species (Carpenter *et al*., 1975). Subchronic treatment of rats by gavage with xylene in corn oil results in enlarged livers and kidneys at doses down to 150 mg/kg-day (Condie *et al*., 1988).

Inhalation exposure of rats to xylene at 1,450 ppm for eight hours, or as low as 800 ppm for 14 hours per day for six weeks caused significant, apparently permanent hearing loss (Pryor *et al.*, 1987). The same type of effect has been observed with toluene, styrene and chlorinated solvents such as trichloroethylene. The effect appears to be selective for mid-frequencies in rats (Pryor *et al*., 1987; Crofton *et al*., 1994). Additive effects have been observed among several ototoxic solvents, rather than synergistic or antagonistic (Rebert *et al*., 1995).

Chronic administration studies were carried out for NTP in both rats and mice (NTP, 1986) using a technical xylene composed of 9% o-, 60% m- and 14% p-xylene, plus 17% ethylbenzene. Xylene was administered by gavage in corn oil at 0, 250 or 500 mg/kg-day in F344/N rats and at 0, 500 or 1,000 mg/kg-day in $B6C3F_1$ mice, five days/week for 103 weeks for both species. Survival was poor in the male rats and dose-related, but many of the early deaths were caused by the gavage administration. Body weights of the high-dose male rats were slightly decreased (5 to 8%) after week 59. The body weights of other rat and all mouse groups were comparable to their respective controls. A brief period of hyperactivity was observed in high-dose mice after dosing beginning after week four, continuing through the end of the treatment period at 103 weeks. These moderate toxicity signs in rats and mice (plus supporting data from shorter-term xylene administrations) were considered to indicate that near maximum-tolerable doses had been achieved. There were no increases in neoplastic nor non-neoplastic lesions in either species that were considered to be xylene-related. U.S. EPA used this study, reported in the "IRIS" database, to derive a reference dose (RfD) for xylene, concluding that the 500 mg/kg-day dose in rats was a LOAEL and 250 mg/kg-day was a no-observed-effect level (NOEL). This was adjusted to daily dosing by multiplying by 5/7 and divided by an uncertainty factor of 100 to obtain the RfD, rounded off to a value of 2 mg/kg-day.

In another chronic study, Maltoni *et al*. (1985) administered 500 mg/kg xylenes by gavage in olive oil to male and female Sprague-Dawley rats for four to five days/week for 104 weeks, observing them until they all had died (141 weeks). No specific tumors were reported to be elevated, but more of the treated female rats bore some type of malignant tumor at death than did controls. Because insufficient study details were provided and it is not considered appropriate to combine tumors of unrelated types for carcinogenicity assessment, this study is considered weak in two scientific reviews, and insufficient evidence of xylene carcinogenicity in rats (NTP, 1986; ATSDR, 1995).

Genetic Toxicity

According to NTP (1986), neither mixed xylene nor any of its individual isomers were mutagenic when tested with and without metabolic activation by the Ames assay in four *Salmonella* strains. Ethylbenzene was tested in cytogenetic assays using Chinese hamster ovary cells with and without activation. There was no increase in sister-chromatid exchange nor chromosomal aberrations. A more recent evaluation of the wide variety of available studies has concluded that xylenes are non-genotoxic both *in vitro* and *in vivo* (ATSDR, 1995).

Developmental and Reproductive Toxicity

Xylene has not been shown to be teratogenic in several studies to date. However, fetotoxicity and delayed maturation have frequently been observed. Mirkova *et al*. (1983) exposed Wistar rats to xylene by inhalation for six hours/day, five days/week from gestation days 1 to 21. Measured

exposure concentrations were 0, 14, 53 and 468 mg/m^3 (0, 3, 12 and 106 ppm). Effects including increased fetal hemorrhages and defects in skull ossification are claimed down to 3 ppm, although the lowest significant effect level is stated as 12 ppm. Increased post-implantation loss (without a decrease in viable fetuses per litter) and decreased body weights at birth, 7 and 21 days were noted at 12 and 106 ppm. The mean weight at birth of controls was 3.64 +/- 0.26 grams and of offspring of dams exposed to 106 ppm was 3.17 +/- 0.24 grams.

Hass and Jakobsen (1993) found delayed ossification of the *os maxillare* in offspring of Wistar rats exposed for six hours/day on gestation days 4 to 20 to 200 ppm xylene, with no effect on ossification of the fontanelles or the sternabrae. The xylene dose to dams was about 130 mg/kg-day. The male offspring of treated dams had slightly higher body weights at birth (6.6 +/- 0.4 grams), with no change in females (6.2 +/- 0.4 grams), compared to controls (males 6.1 +/- 0.4 grams; females 6.1 +/- 0.5 grams). There was no effect on live fetuses per dam or pre- or post-implantation loss. Postnatally, the treated offspring also tended toward body weights greater than controls, with significantly increased weights of both sexes at 28 days. The offspring had slightly impaired rotarod performance when tested at about three weeks of age. Treated females were able to stay significantly fewer seconds on the rotarod on day 22 and 23, but matched controls on day 24. Male rats were slightly better than controls on day 22, significantly worse on day 23 and slightly better on day 24. Similar but slightly more severe performance deficits were observed on rat offspring of mothers exposed to 500 ppm xylene for 6 hr/day on gestation days 7-20 in a followup study (Hass et al., 1995).

Hass and Jakobsen concluded that "Altogether, in the present studies serious birth defects after exposure to technical xylene throughout the prenatal development such as reported in another study (Mirkova *et al*., 1983) were not observed, although the exposure level was substantially higher. However, the exposure level of 200 ppm should not be regarded as a no-observed-effect level for pregnant rats, since some exposure-related changes were observed especially in the postnatal development of the offspring." The authors did not comment on the much lower weights of the neonates in the Mirkova study, compared to their own, which may indicate some significant nutritional or husbandry differences. Poor conception rates and a high incidence of fetal hemorrhage in controls were noted as further evidence of s such differences (ATSDR, 1995).

The weight-of-evidence appears to indicate that the behavioral neurotoxic effects of xylene are direct effects on fetal development, but that any structural fetotoxic effects of xylene are secondary to maternal toxicity. Xylene does not appear to be a selective teratogen. The possibility of fetotoxic effects from concentrations to which humans would be exposed in the workplace seems slight (Brown-Woodman *et al*., 1991; 1994). However, even higher concentrations and doses may sometimes occur in solvent abuse, and the possibility of fetotoxic exposures and effects cannot be excluded (ATSDR, 1995).

Carcinogenicity

There have been several epidemiological studies relevant to potential carcinogenic effects of xylenes in humans. Such studies tend to involve exposures to many different solvents over a career of occupational exposures and so have little power to discriminate among solvents for long-term effects. Some small studies have suggested a possible relationship (Arp *et al*., 1983; Wilcosky *et al*., 1984) between occupational xylene exposure (primarily by inhalation) and leukemia, but their limitations preclude any conclusion. No animal studies on cancer using an inhalation route are available. Analyses of larger populations of solvent-exposed workers show only minor trends

in cancer mortality, compared to controls, except for an increased rate of leukemia ascribable to benzene exposure (Berlin *et al*., 1995; Chen and Seaton, 1996).

Chronic studies of xylene in F344/N rats and B6C3F1 mice by gavage in corn oil were carried out by NTP (NTP, 1986). After range-finding studies, 50 males and females of each species were administered mixed xylene (9% o-, 60% m-, 14% p-xylene and 17% ethylbenzene) five days/week for 103 weeks at doses of 0, 250 or 500 mg/kg for rats and 0, 500 or 1,000 mg/kg for mice. There was excessive mortality in male rats which appeared to be gavage-related. Mean body weights were reduced in high-dose male rats by 5 to 8% after the 59th week, but were not significantly different from controls in other treatment groups. There was no increased incidence of tumors at any site in either sex of both rats and mice. There were also no dose-dependent non-neoplastic lesions, although 5 to 30 minutes of hyperactivity was observed after daily dosing in the high-dose mice beginning after week four and continuing through the treatment duration. NTP reviewers concluded that there were no data discrepancies that would influence the final interpretation and that the results therefore show no evidence of carcinogenicity for xylene in both rats and mice under the conditions of this test.

U.S. EPA concluded that xylene is a noncarcinogen and categorized it as a "D," meaning that there is no evidence of carcinogenicity in either human or animal studies.

Toxicological Effects in Humans

Acute Effects

Exposure to xylene vapors is annoying to most people and can cause irritation of the nose and throat at 100 to 200 ppm (ATSDR, 1995). Severe pulmonary irritation does not occur until much higher concentrations (several thousand parts per million) are reached. No acute effects were observed on several sensitive behavioral tests with four hours exposure to 70 ppm xylene (Olson *et al.*, 1985). Occupational exposures to 100 to 200 ppm have been observed to have very slight acute neurological effects. Some behavioral parameters may be increased and others decreased. It was inferred that the dose achieved with several hours of 100 ppm to 200 ppm exposures was either mildly stimulating or mildly sedative (Laine *et al*., 1993; Savolainen *et al*., 1985a,b). Rapid recovery from such effects is expected as the dose is eliminated, mostly by metabolism but also partly by exhalation (Kawai *et al*., 1991; Inoue *et al*., 1993). These effects and time course are similar to the observations in rats using sensitive neurophysiological assays (Dyer *et al*., 1988).

Subchronic Effects

With longer-term exposures, persistent mild-to-moderate neurological effects have been reported from exposures to xylene alone or to mixed solvents (Uchida *et al*., 1993; Ruijten *et al*., 1994). In the most detailed investigation (Uchida *et al*., 1993), Chinese factory workers with long-term exposures (average seven-year employment in their plants) to xylene in air reported several physical symptoms at higher rates than did controls in a 69 item interview questionnaire. Significantly increased symptoms reported during work included eye irritation, nasal irritation, sore throat and a floating sensation. They reported having, during the last three months, significantly more nausea, nightmares, anxiety, forgetfulness, inability to concentrate, postural hypotension, poor appetite, reduced grasping power, reduced muscle power in extremities and rough skin compared to controls. None of the signs and symptoms were confirmed by objective measures.

The exposed group was selected from personnel in the factories whose passive monitors showed significant xylene content at the end of a work shift (arithmetic mean 21 +/- 22 ppm, SD; geometric mean 14.2 +/- 2.6 ppm, GSD), while controls were selected from clerical workers in the same factories (Uchida *et al*., 1993). There was no indication of solvent-related effects on clinical or hematology parameters. A significant increase in serum enzymes derived from the liver was interpreted by the authors as not being clinically significant. The effects do not seem consistent with the low measured xylene concentrations in air. The indicated mean levels are below acute systemic-effect levels reported by other workers, but are consistent with acute effect levels reported in similar studies by the same authors (Chen *et al*., 1994). The possibility of biased reporting exists with a questionnaire format and three-month symptom recalls are widely considered to be unreliable. We therefore judge that these data are indicative of a potential long-term effect, but would be inconclusive without further supporting evidence of neurologic effects from occupational exposures to aromatic solvents.

Because most occupational exposures are to mixed solvents, or to many different solvents over an extended time period, it is difficult to ascribe particular effects to specific agents. There is an extensive literature on reported adverse neurological effects from subchronic to chronic solvent exposures, such as Hogsted (1994), Hooisma *et al*. (1994) and Grosch *et al*. (1996). Xylenes are often components of the paint and cleaning solvents mentioned in these reports. Nevertheless, there is no direct evidence to indicate xylene involvement in this solvent syndrome, except that xylene would be expected to have additive neurological (and liver) effects with many of the other solvents.

Genetic Toxicity

Richer *et al*. (1993) studied cytogenetic effects of xylene and toluene in human lymphocytes *in vivo* and *in vitro*. They found no effects of three-day exposures for seven hours/day, repeated three times over two weeks, to xylene at 40 ppm in air, toluene at 50 ppm or both solvents together at these levels, on sister-chromatid exchange, cell cycle delay and cell mortality. *In vitro* exposures for 72 hours at up to 2 mM xylene also showed no effects on these parameters; higher levels caused cell mortality. These data provide no evidence of genetic toxicity under conditions relevant to human environmental or occupational exposures.

Developmental and Reproductive Toxicity

Xylene exposure in women of child-bearing years who are employed as histological technicians has been of concern for several years, because of the chronic exposures and potential for reproductive toxicity of xylene. A 1992 study of this population did not reveal any neurobehavioral effects (Kilburn and Warshaw, 1992), probably indicating relatively moderate exposure levels. However, in a study with 535 women (206 cases and 329 referents), spontaneous abortions appeared to be increased among the women working in pathology and histology laboratories (Taskinen *et al*., 1994). Significant associations with spontaneous abortion were found for exposure to toluene (odds ratio 4.7, 95% CI 1.4 to 15.9), xylene (odds ratio 3.1, CI 1.3 to 7.5) and formaldehyde (odds ratio 3.5, 95% CI 1.1 to 11.2) three or more times a week, adjusted for covariates. No association of these exposures with congenital malformations of their offspring was found.

In a retrospective study of fertility rates among women exposed to various solvents, a significantly reduced fertility rate was also observed (Sallmen *et al*., 1995). Rates were decreased among women who were exposed to solvents in shoe factories, dry cleaning shops and in the metal

industry. Further, more specific exposure evaluations are necessary to determine whether there is a direct relationship between exposure to xylene and decreased fertility rates.

Immunotoxicity

Very few studies have been conducted with specific measurements of immune parameters and these are for mixed exposures to benzene, toluene and xylene; some decreases were observed. The cytogenetic study of Richer *et al*. (1993) on human lymphocytes *in vivo* and *in vitro* indicated no relevant effects of xylene on sister chromatid exchanges and cell cycle delay, while cell mortality was altered only *in vitro* at high concentrations. There is no indication of depressed immune systems in workers chronically exposed to organic solvents, as reflected in their mortality statistics (Berlin *et al*., 1995; Chen and Seaton, 1996). Animal studies have observed depressed immune system markers or responsiveness only at high doses of xylene, appearing to be secondary to effects on other organs (ATSDR, 1995). Based on these data, it appears that the immune system is not a target tissue for xylene toxicity.

Neurotoxicity

The nervous system is an important target for xylene toxicity. Evaluation of xylene effects should distinguish between effects secondary to annoyance related to its odor, acute systemic disinhibitory and sedative signs and symptoms similar to those caused by many other organic solvents, and longer-term systemic effects potentially related to neuropathology. Acute behavioral effects of xylene may occur at levels approximating 14 ppm (Uchida *et al*., 1993), associated with headaches and irritation of eyes, throat and nose (the assay for xylene concentration in air was poorly documented in this study and may be questionable). In another study, painters reported shortness of breath with 0.5 to 1.5 hours exposure to about 500 ppm combined toluene and xylene. With more prolonged exposures, a significant increase in multiple acute symptoms was observed (combined median levels of the two solvents for eight hours was approximately 166 ppm with a range of eight-hour TWAs of 25 to 1,000 ppm) (Wang and Chen, 1993). As measured by functional tests in a study using volunteers, the threshold for systemic behavioral effects of xylene appeared to be around 200 ppm (5 mg/kg-hour) with two or more hours of exposure (Savolainen *et al*, 1985a,b; Laine *et al*., 1993).

Occupational exposures to xylene have also been associated with chronic neurological effects. In a paradigm-defining exposure, a workman who had several months of heavy exposure to “near-pure” xylene was observed to suffer from a variety of neurological symptoms, including tiredness, irritability, dizziness, agitation, lightheadedness, impaired concentration and memory, confusion, tremor, hyperreflexia and unstable gait (Roberts *et al*., 1988). Workers exposed to xylene for a median of about seven years in production of rubber boots or plastic-coated wire reported significantly greater adverse health symptoms over the last three months than did control workers (Uchida *et al*., 1993). Personal monitoring devices at the time the survey was administered showed relatively low xylene concentrations in the breathing zone (i.e., a geometric mean of 14 ppm and an arithmetic mean of 22 ppm over an eight-hour period). Symptoms reported to be increased included anxiety, forgetfulness, inability to concentrate, poor appetite and reduced muscle power in extremities. Because three-month symptom recalls are unreliable and there was no objective confirmation of the reported symptoms, this report is considered weak evidence of chronic neurological effects. In addition, the xylene exposure concentrations are uncertain because of the absence of measurements during the chronic exposures and questionable assay techniques. This study is one of the few investigations of specific exposure to xylenes, rather than mixed solvents.

Gupta *et al.* (1990), in an occupational epidemiological study on 50 varnishing workers exposed to a mixture of toluene (mean 32 ppm) and xylene (mean 38 ppm), reported impairment of immediate and delayed memory. Kilburn and Warshaw (1992 and earlier studies) found that female histology technicians exposed to formaldehyde and organic solvents including xylene reported sleep and memory disturbances, disequilibrium and decreased dexterity. However, this could not be clearly associated with xylene exposure. Ruijten *et al.* (1994) studied the neurobehavioral effects of xylene and other solvents in shipyard spray painters, compared to other manual workers. A major part of the painters' work involved exposure in confined spaces to vapors from paints containing greater than 50% xylene. These workers had complained of dizziness, drowsiness and mood changes. Their solvent exposures were confirmed by urinary monitoring, but no air measurements were reported. Symptom questionnaires, measurements of sensory and motor nerve parameters and function tests were administered. The questionnaires revealed significant presumably solvent-related symptoms, including mood changes, equilibrium complaints and fatigue. Some peripheral nerve conduction velocities were slowed and amplitudes were decreased. Performance of a hand-eye coordination task was significantly depressed, as was a symbol digit substitution test and a word vigilance task. A memory test on exposed subjects showed no changes, relative to the controls. Many other studies reveal apparent effects of the same types from long-term exposures to organic solvent mixtures, often but not exclusively containing toluene, xylene and/or ethylbenzene. Taken as a whole, these studies support the premise that there is a common neurobehavioral syndrome associated with prolonged, excessive aromatic solvent exposure that should be addressed in setting protective levels for the common aromatic solvents (Brackbill *et al.*, 1990; Bleeker *et al.*, 1991; Wang and Chen, 1993; Baker, 1994; Hogstedt, 1994; Hooisma *et al.*, 1994; Bolla *et al.*, 1995; Grosh *et al.*, 1996).

Carcinogenicity

Epidemiological studies on chronic exposures to solvents generally involve concurrent or sequential exposures to many chemicals over a working lifetime and it is difficult to distinguish among potential effects of different solvents. This is particularly true for xylene because it is commonly used in mixtures with other solvents, especially the aromatics benzene, toluene and ethylbenzene and has physical properties similar to these chemicals. Therefore, "pure" occupational exposures are rather limited. Some small studies have suggested a possible relationship (Arp *et al.*, 1983; Wilcosky *et al.*, 1984) between inhalation exposure to xylene and leukemia, but their limitations preclude conclusions. In mixed exposures, leukemia, if elevated, tends to be attributed to benzene, as in the studies of Chen and Seaton (1996). Cancers of the lymphohematopoietic system and the uterine cervix appeared to be slightly elevated in one study of people with high exposures to solvents (Berlin *et al.*, 1995). Total cancers were not significantly elevated and overall mortality was close to controls; deaths due to cardiovascular disease were significantly decreased. The U.S. EPA classification of xylene as "D," for "inadequate or no human and animal evidence of carcinogenicity," seems appropriate following our review of the available studies.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Chronic neurobehavioral effects are the noncancer endpoint of most significance. Sensitive behavioral measures often find effects at about 100 to 200 ppm in air after acute inhalation

exposures of about two hours or more in both animals and humans. There are no applicable subchronic or chronic animal studies with measurements of the more sensitive neurobehavioral endpoints, nor are there relevant studies involving administration of xylene in drinking water. Therefore, the acute human inhalation exposures and human epidemiological studies must be relied on for dose-response extrapolations. The epidemiological studies provide the most sensitive endpoints, but the exposure concentration data are generally quite limited and are inadequate for benchmark exposure calculations.

The epidemiological evaluations indicate that chronic exposures to xylene in the 10 to 50 ppm range are associated with long-term effects (Kilburn *et al*., 1985; Gupta *et al*., 1990; Bleeker *et al*., 1991; Uchida *et al*., 1993). We choose to use the study of Uchida *et al*. for health risk assessment, while recognizing that both the effects and the exposure concentrations might be overstated. Thus dividing by very large uncertainty or safety factors to ensure protection would be inappropriate.

Uchida *et al*. report a variety of acute and chronic effects in solvent workers exposed to a mixture of solvents composed of 70% or more of xylenes. Eight-hour TWA exposures up to 175 ppm were found, with a geometric mean TWA of 14 ppm and an arithmetic mean of 21 ppm. The percent of total positive responses to questions about subjective symptoms over the last three months, with number of individuals in parentheses, is shown in Table 1.

Table 1. Percent of Total Positive Responses

	Controls	**1-20 ppm**	**>21 ppm**	**Total exposed**
Men	5.9 (116)	13.8 (67)	12.4 (40)	13.3* (107)
Women	7.3 (125)	16.6 (38)	13.1 (30)	15.0* (68)
Combined	6.6 (241)	14.8 (105)	12.7 (70)	14.0* (175)

* $p < 0.01$

It should be emphasized that the percentages above are calculated based on all answers that were positive on a 59-symptom list, not the percent of individuals reporting symptoms. Most people in control and exposed groups reported at least one symptom; 25% more of the exposed individuals reported a high number of symptoms than did controls (a significant increase). The lack of a dose-response relationship in Table 1 might indicate that the limited air sampling did not adequately differentiate among chronic exposure levels. It might also indicate the presence of a non-biological explanation for the increased reports of symptoms, such as recall bias. Incidence of several acute symptoms (eye irritation, sore throat and floating sensation) did exhibit the expected dose-response with air levels of xylene measured at that time. There was no attempt to evaluate severity of symptoms. Considering the relatively low (increased) prevalence of people reporting multiple symptoms (25%) and the mild, not clinically confirmed nature of the effects, this report will be considered to provide an LOAEL which is fairly close to an NOAEL. A low uncertainty factor for the conversion of an LOAEL to an NOAEL is therefore justified.

There was also an increased prevalence of cases with mild liver dysfunction among the exposed individuals in the study of Uchida *et al*., as determined by the serum levels of several liver markers. Because of the minimal changes and the lack of consistency of changes in these enzymes in other

solvent studies, this was assumed by the authors to be insufficient evidence of an adverse effect on the liver. We consider this as an appropriate interpretation.

Carcinogenic Effects

Xylene is not considered a carcinogen and there are no data which are appropriate for estimating potential carcinogenic potency.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens 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, for preparing foods and beverages and for bathing or showering. It is also used for washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures.

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

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

where,

NOAEL	=	No-observed-adverse-effect-level (in mg/kg-day)
BW	=	Body weight (in kg)
RSC	=	Relative source contribution (dimensionless)
UF	=	Uncertainty factor (product for human variability, inter-species extrapolation and data insufficiencies)
L/day	=	Volume of water consumed per day (in L/day).

There are two exposure measures in these equations, the relative source contribution (RSC) and the water consumption rate. The RSC is based on an estimate of the contribution of drinking water relative to other sources of exposure to the chemical contaminant. The other sources are food, air, soil contact, occupational exposures and exposure through smoking. Often food is the most significant source of exposure to a chemical in addition to drinking water exposure. The RSC default used by U.S. EPA and the Office of Environmental Health Hazard Assessment (OEHHA) is 20% based on the assumption that drinking water makes up 20% of the exposure to the chemical. U.S. EPA restricts RSC values to a range of 20% to 80% in performing their calculations of negligible risk drinking water levels or Maximum Contaminant Level Goals (MCLGs) (U.S. EPA, 1992b).

In the case of volatile solvents like xylene, dietary exposures are expected to be negligible. Xylene is not detectable in plant foods, as discussed earlier, and was reported in only one study at low levels in a meat product (fish). For the present case, the RSC from drinking water will be assumed to be 40% (0.4) based on known (low) exposures to trace levels of xylene in air and the variable exposure to xylene from other household uses.

The other exposure factor in the equation, water intake (in L/day), represents the amount of tap water which an individual consumes as drinking water as well as mixed with beverages and used in cooking. The adult default for this factor is 2 L/day at an assumed body weight of 70 kg. For small children, 1 L/day is used, based on a 10 kg body weight.

For xylene, dermal absorption could theoretically contribute to the total dose from exposure to the solvent in water in bathing or swimming as well as from occupational or home solvent usage. Inhalation of xylene released from tap water in its normal household use may also contribute to exposure. An equivalent amount of exposure will be added to the water intake in liter equivalents per day (L_{eq}/day). For example, if it were estimated that bathing and/or showering could add an exposure equivalent to drinking 2 L/day, then the total would be 4 L_{eq}/day to account for both drinking and bathing or showering in the equation to calculate the PHG. In the past U.S. EPA has considered only ingestion of drinking water in calculating negligible risk levels for chemical contaminants (except for radon), although the Agency has informally proposed a default of 2 L_{eq}/day for showering exposure based on an overall average of many volatile organic compounds (VOCs) studied. This value will be used for the present analysis. Therefore, substituting L_{eq}/day for the L/day term in the above formula, the value of 4 L_{eq}/day is incorporated into the calculation.

The uncertainty factors used in this analysis are consistent with current U.S. EPA and OEHHA practices, which more specifically acknowledge actual uncertainty in data extrapolations. For the critical effect in this case, self-reported neurological symptoms at daily time-averaged occupational exposure levels of 14 ppm (geometric mean, equivalent to 62 mg/m^3), an uncertainty factor of three is used to estimate an NOAEL from an LOAEL and another factor of 10 is used to account for potential sensitive individuals or populations. Therefore, the combined uncertainty factor is 30.

The daily xylene dose for an adult male (in mg/kg-day) in the Uchida *et al*. (1993) study is assumed to be:

$$\frac{62\ \text{mg/m}^3\ \text{X}\ 10\ \text{m}^3\text{/day}\ \text{X}\ 6/7\ \text{days/week}}{70\ \text{kg body weight}} = 7.5\ \text{mg/kg-day}$$

In this estimate, the volume of air breathed during a working day and the body weight are calculated using OEHHA default values. The estimated dose would be 450 mg/day for a 60 kg person and 525 mg/day for a 70 kg person. The occupational exposure is assumed to be six out of seven days per week because this is the standard working week in mainland China. The public health-protective concentration of contaminant in drinking water, C, is then calculated as:

$$C = \frac{7.5\ \text{mg/kg-day} \times 70\ \text{kg} \times 0.4}{30 \times 4\ L_{eq}\text{/day}}$$

$$= 1.8\ \text{mg/L} = 1.8\ \text{ppm}$$

Thus, OEHHA calculates a PHG of 1.8 mg/L (1.8 ppm) for xylenes in drinking water.

RISK CHARACTERIZATION

A major limitation of this calculation could be said to be the uncertainty of the neurological effects from chronic exposures in the Uchida *et al*. (1993) study, since these were self-reported,

unverified effects. However, because several other studies have reported objectively verified effects under similar circumstances of long-term exposure to mixed aromatic solvents (often toluene and xylene), we conclude that the effects from the more "pure" exposures to xylene in this case are likely to be real. These data should therefore be used in the PHG calculation.

The method used here to estimate a public health-protective PHG for xylene in drinking water includes several minor changes from risk assessment methods used previously. These include using a factor of less than 10 for conversion of a LOAEL to a NOAEL based on less severe toxicity endpoints; using a 40% RSC instead of 20%, for the relatively smaller contribution of exposure to xylene from foods; and considering potential inhalation and dermal absorption routes of exposure to VOCs in water, in addition to the exposure by drinking the water. The combination of these three changes produces an estimated public health-protective PHG which is comparable to the State MCL of 1.75 ppm (DHS, 1987) and lower than the current U.S. EPA estimate of 10 ppm, both of which were based on a chronic toxicity study in rats. ATSDR (1995) has estimated a "safe" oral exposure level of 0.2 mg/kg-day, which would be equivalent to 7 mg/L (ppm) maximum residue level in water before any correction for other exposure sources, if applicable. We believe OEHHA's value of 1.8 mg/L (1.8 ppm) is more appropriate because it is based on a human study, it considers more of the probable exposure pathways and it is more consistent with recent risk assessment guideline proposals from U.S. EPA and OEHHA.

Although infants and children can be more sensitive to certain types of neurological effects than adults, use of an uncertainty factor of 30 from the mean levels in chronic exposures should be adequate to provide protection in this case. No extra sensitivity of infants and children is expected. Effects of xylene are generally additive with other aromatic solvents (Olson *et al.*, 1985; Pathiratne *et al.*, 1986; Pryor *et al.*, 1987; Richer *et al.*, 1993; Rebert *et al.*, 1995). Because mixtures of toluene, xylene, and ethylbenzene are common, and their residues are also found together in the environment, additivity should be considered in setting regulatory limits for the aromatic solvents in drinking water, based upon their respective PHG values.

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