2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ETHYLBENZENE IN THE UNITED STATES

Ethylbenzene is widely distributed in the environment. It is primarily used for the production of styrene, which is the monomeric unit for polystyrene materials. Ethylbenzene is also used as a solvent and in the manufacture of several organic compounds other than styrene; however, these uses are very minor in comparison to the amounts used for styrene production. The production volume of ethylbenzene is typically among the highest of all chemicals manufactured in the United States. In 2005, nearly 12 billion pounds of ethylbenzene were produced domestically, with historical levels ranging anywhere from approximately 7 to 13 billion pounds annually. Routine human activities, such as driving automobiles, boats, or aircraft, or using gasoline powered tools and equipment, release ethylbenzene to the environment. Environmental and background levels of ethylbenzene are generally small and therefore, have minimal impact on public health. Trace levels of ethylbenzene are found in internal combustion engine exhaust, food, soil, water, and tobacco smoke, but usually at levels well below those that have been shown to exhibit toxic effects in laboratory animals or human exposure studies.

Ethylbenzene is not considered highly persistent in the environment. It partitions primarily to air and removal via photochemically generated hydroxyl radicals is an important degradation mechanism. The half-life for this reaction in the atmosphere is approximately 1–2 days. Biodegradation under aerobic conditions and indirect photolysis are important degradation mechanisms for ethylbenzene in soil and water. Based on a vapor pressure of 9.53 mm Hg and Henry's law constant of $7.9x10^{-3}$ atm-m^3/mol, volatilization from water and soil surfaces is expected to be an important environmental fate process for ethylbenzene. If released to soil, ethylbenzene is expected to possess moderate mobility based on a soil adsorption coefficient (K_{oc}) value of 240.

Ethylbenzene is ubiquitous in ambient air, primarily as a result of automobile emissions. The median level of ethylbenzene in city and suburban air was reported as 2.7 μg/m^3 (0.62 ppb). In contrast, the median level of ethylbenzene measured in rural locations was 0.056 μg/m^3 (0.013 ppb). Ethylbenzene levels in indoor air tend to be higher than corresponding levels monitored in outdoor air, as a result of contributions from environmental tobacco smoke (ETS) and various consumer products, in addition to the permeation indoors of ethylbenzene from outside air. A study analyzed the components of ETS for the 50 top-selling U.S. cigarette brand styles in 1991 and for the University of Kentucky Research cigarette, K1R4F. The ethylbenzene concentrations measured were 8.68 μg/m^3 for full-flavor cigarettes,

8.24 μg/m^3 for full-flavor, low-tar cigarettes, and 8.72 μg/m^3 for ultra-low-tar cigarettes. The mean ethylbenzene concentration for all cigarettes was 8.50 μg/m^3. A study reported a maximum outdoor air concentration of 7.4 μg/m^3 (1.7 ppb) for ethylbenzene at four residential locations, while indoor air concentrations at these same homes ranged from 5 to 110 μg/m^3 (1–25.3 ppb). Ethylbenzene is detected infrequently in surface water. Data from the EPA STOrage and REtrieval Database (STORET), indicated that ethylbenzene was detected in <3% of the surface water samples analyzed in the United States from January 2005 to March 2007, with a maximum concentration of 2 ppb.

Ethylbenzene was identified in 82 different food items at a maximum concentration of 0.129 ppm in data obtained from the FDA Total Diet Study Market Basket Surveys collected between September 1991 and October 2003. Trace concentrations of ethylbenzene have been reported in split peas (0.013 mg/kg [ppm]), lentils (0.005 mg/kg [ppm]), and beans (mean concentration 0.005 mg/kg [ppm]; maximum concentration 0.011 mg/kg [ppm]).

The general population is primarily exposed to ethylbenzene from the inhalation of ambient air. This is due to the direct release of ethylbenzene into the air by the burning of fossil fuels or industrial processes, and partitioning into the air from other media (e.g., soil, surface water). This partitioning of ethylbenzene into the air or water would play a role in exposure to populations living near hazardous waste sites. In addition to inhalation exposure, ingestion of ethylbenzene may also occur because trace amounts have been found in water supplies and various food items.

2.2 SUMMARY OF HEALTH EFFECTS

In humans, eye irritation was observed after exposure to 10,000 ppm ethylbenzene for a few seconds. Volunteers reported irritation and chest constriction after acute-duration exposures to 2,000 ppm ethylbenzene. These symptoms worsened as the concentration was increased to 5,000 ppm. Human exposures in the range of 2,000–5,000 ppm ethylbenzene were associated with dizziness and vertigo. Complete recovery occurs if exposure is not prolonged. Momentary ocular irritation, a burning sensation, and profuse lacrimation were observed in humans exposed to 1,000 ppm ethylbenzene. Workers exposed occupationally to solvent mixtures that included ethylbenzene showed an increased incidence of hearing loss compared to unexposed individuals. Respiratory effects were not observed in two patients exposed to 55.3 ppm ethylbenzene for 15 minutes. An increase in the mean number of lymphocytes and a decrease in hemoglobin levels were observed during a 1-year period in workers exposed chronically to solvents including ethylbenzene. However, no adverse hematological effects were observed in workers

exposed to ethylbenzene for 20 years. Although no information on ethylbenzene concentrations was reported, an estimated concentration of 6.4 mg/m^3 was derived from a mean post-shift in urinary mandelic acid concentration in workers, based on the relationship between ethylbenzene concentrations in air and urinary mandelic acid concentration in a chamber-exposed group. No liver lesions or differences in liver function tests between exposed and nonexposed workers were observed and no cases of malignancy in workers were reported. However, given the low exposure concentration, this study had limited the power to detect any effect. No other studies in humans exposed to ethylbenzene were located. Given that little data in humans are available, it is assumed that adverse effects observed in animals are relevant to humans.

Acute-duration and intermediate-duration studies in animals suggest that the auditory system is a sensitive target of ethylbenzene toxicity. Significant losses of outer hair cells (OHCs) in the organ of Corti have been observed in rats after acute-duration exposure ≥400 ppm and intermediate-duration inhalation exposure to ≥200 ppm ethylbenzene. These OHC losses have been observed up to 11 weeks after termination of the exposure, suggesting that these effects may be irreversible. Significant deterioration of auditory thresholds is also observed in animals affected with OHC losses. Auditory deficits have also been observed in animals after an intermediate-duration oral exposure to ethylbenzene. An almost complete loss of the three rows of outer hair cells in the organ of Corti was observed in rats 10 days after the last dose (900 mg/kg/day) in an acute-duration study. Effects on the central nervous system, such as moderate motor activation, narcotic effects, changes in posture and arousal, and salivation and prostration have been observed in animals after acute- and intermediate-duration exposure to ≥400 ppm ethylbenzene.

Results of 4- and 13-week studies indicate that intermediate-duration oral exposure to ethylbenzene produces effects to the liver. Effects indicative of liver toxicity observed included increased activity of serum liver enzymes (alanine aminotransferase [ALT] and gamma-glutamyltransferase [GGT]) in males (≥250 mg/kg/day) and females (750 mg/mg/day), increased absolute and relative liver weights (≥250 mg/kg/day in males and females), and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy (≥250 mg/kg/day in males and females). Increased bilirubin (≤250 mg/kg/day in males and 750 mg/kg/day in females), total protein (750 mg/kg/day in females), albumin (750 mg/kg/day in males and females), globulins (750 mg/kg/day in females), and cholesterol (≤250 mg/kg/day in males and females), and decreased prothrombin time (750 mg/kg/day in males and ≥250 mg/kg/day in females) were considered by study investigators as adaptive effects in the liver. In males in the 75 mg/k/day group, relative liver weight was significantly increased by 4% compared to controls; however, no

histopathological changes, or increases in absolute liver or serum liver enzyme activities were observed at this dosage. Given that ethylbenzene is a microsomal enzyme inducer, and the absence of histopathology and other evidence of liver injury at the 75 mg/kg/day dosage, the small increase in relative liver weight in male rats was at this dosage not considered evidence for an adverse effect on the liver. Results of the 4-week gavage study in rats were similar to those of the 13-week study, identifying no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values of 250 and 750 mg/kg/day, respectively, for liver effects. Observed effects consistent with hepatotoxicity included increased absolute and relative liver weights (≥250 mg/kg/day in males and 750 mg/kg/day in females), increased incidence of hepatocyte centrilobular (≥250 mg/kg/day in males and 750 mg/kg/day in females), and increase serum liver enzyme activity (ALT) (750 mg/kg/day in males and females). Histopathological changes characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight were observed in female rats administered 408 mg/kg/day by gavage for 6 months. No other hepatic changes were reported. No liver effects were observed in female rats administered 136 mg/kg/day. However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

Guinea pigs exposed to sublethal concentrations of ethylbenzene (≤10,000 ppm for <100 minutes) showed “moderate” pulmonary edema and congestion. These findings had disappeared in animals after a 4–8-day recovery period, suggesting that these pathological effects in the lung are reversible. A 50% respiratory depression was observed in mice exposed to ≥1,432 ppm for 5–30 minutes. Respiratory depression has not been reported in humans exposed to ethylbenzene. Nasal and eye irritation was evident in animals exposed to 1,000 ppm for ≥3 minutes. One study did not observe weight or histopathological effects in the lungs of rats or mice exposed to 782 ppm or rabbits exposed to 1,610 ppm ethylbenzene for 4 weeks. Absolute and relative lung weight was increased in rats, but not mice, exposed to ≥250 ppm for 13 weeks; no treatment-related histopathological effects were observed. One study did not report pulmonary injury in rats, guinea pigs, rabbits, or monkeys exposed to 600–2,200 ppm ethylbenzene for approximately 6 months; however, only two animals were used in some of the dose groups in rabbits and monkeys. No treatment-related histopathological effects were noted in respiratory tissue in rats or female mice exposed to up to 750 ppm ethylbenzene for 2 years. Although an increase in alveolar epithelial hyperplasia was noted in male mice in the 750-ppm group the incidence fell within historical controls for the conducting laboratory. The available data on adverse respiratory effects associated with ethylbenzene exposure in animals and the limited data available in humans suggest that respiratory effects in humans could result following inhalation exposure to high concentrations of

ethylbenzene. Respiratory effects from low-level exposure, such as that found in the outdoor air, appear to be less likely.

Developmental effects have been reported in the offspring of pregnant animals exposed to ethylbenzene during gestation. The best reported studies available suggest that developmental effects are generally observed at concentrations of approximately ≥1,000 ppm. Significant increases in the incidence of fetal skeletal variations were observed in the offspring of pregnant rats exposed to 2,000 ppm and reductions in fetal body weight were observed in the offspring of pregnant rats exposed to ≥1,000 ppm ethylbenzene during gestation. Maternal toxicity, manifested as reduced body weight gain, was also observed in rats exposed to ≥1,000 ppm. No developmental effects were observed at concentrations of ≤500 ppm. In contrast, an increased incidence of fetuses with extra ribs was observed in the offspring of rats exposed to 100 ppm during gestation, but not when the animals were exposed to 100 ppm during pre-mating and gestation. No other significant increases in major malformations or minor anomalies were observed. Neurodevelopmental assessments conducted on F2 rat offspring indicated no effects in a functional observational battery assessment, fore- or hind-limb grip strength, swimming ability, motor activity, startle response, or learning and memory assessments at 500 ppm.

The number of implantations or live fetuses per litter and the percentage of resorptions or non-live implants per litter were unaffected in pregnant rats exposed to 2,000 ppm ethylbenzene during gestation. In a two-generation study, estrous cycle length was significantly reduced in F0, but not F1, females exposed to 500 ppm or in rats or mice exposed to 975 ppm ethylbenzene for 90 days. Reproductive parameters were not affected in F0 or F1 males or females at 500 ppm ethylbenzene. Exposure of rats and rabbits to 100 or 1,000 ppm ethylbenzene for 3 weeks during prior to mating or gestation or both resulted in no conclusive evidence of reproductive effects in either species. Assessments of reproductive organs conducted following intermediate- and chronic-duration exposure to ethylbenzene have not observed histopathological changes in the testes of rats, mice, or rabbits exposed to concentrations as high as 2,400 ppm ethylbenzene for 4 days or in rats or mice exposed to 782 ppm ethylbenzene or rabbits exposed to 1,610 ppm for 4 weeks. No effect was observed on spermatid counts, sperm motility, weight of the caudal epididymis, or testicular morphology in rats or mice exposed to 975 ppm ethylbenzene for 90 days. No adverse histopathological effects were seen in the testes of rats or guinea pigs exposed to concentrations up to 1,250 or 600 ppm, respectively, for 6–7 months.

Other systemic effects have been observed in animals after acute-, intermediate-, and chronic-duration exposures to ethylbenzene. Eye irritation and lacrimation have been observed after acute-duration

exposures in rats, mice, and guinea pigs exposed to ≥1,000 ppm ethylbenzene. Lacrimation was observed in rats exposed to 382 ppm for 4 weeks. In contrast, no ocular effects were seen in rats or mice after a 13-week exposure to 975 ppm ethylbenzene. Mild irritation, reddening, exfoliation, and blistering have been reported in rabbits when ethylbenzene was applied directly on the skin. Slight irritation of the eye and corneal injuries were observed in rabbits when ethylbenzene was instilled onto the eyes.

One study examined the possible association between occupational exposure to ethylbenzene and increased cancer risk; no cases of malignancy were observed in workers exposed to ethylbenzene for 20 years. Animal studies have found increased incidences of neoplasms in rats and mice following inhalation or oral exposure, which are considered relevant to humans. The inhalation studies found clear evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasm's and testicular adenomas, some evidence of carcinogenic activity in female rats based on increased incidences of renal tubule adenomas, some evidence of carcinogenic activity in male mice based on increased incidences of alveolar/bronchiolar neoplasms, and some evidence of carcinogenic activity in female mice based on increased incidences of hepatocellular neoplasms. In a reevaluation of the histopathology of rat kidneys from the NTP study, a study confirmed the NTP findings and suggested that the increased incidence of kidney tumors in rats in the high-dose group was related to a chemical-induced exacerbation of chronic progressive nephropathy (CPN) with a minor contributing factor in male rats being $\alpha_{2\mu}$-globulin nephropathy. The author suggests that since CPN is an age-related disease of rodents without a counterpart in humans, the kidney results of the NTP study are not relevant to humans for risk assessment purposes. However, in an analysis of the association between CPN and renal tubule cell neoplasms in male F344 rats, a study concluded that the association between CPN and renal tubule cell neoplasms is marginal. Results of this analysis suggest that the number of renal tubule cell neoplasms secondary to CPN would be few. An increase in the total number of malignant tumors was observed in rats orally exposed to ethylbenzene; however, data on specific tumor types were not provided. On the basis of the NTP study, IARC has classified ethylbenzene as a Group 2B carcinogen (possibly carcinogenic to humans). In the most recent carcinogenicity assessment by the EPA conducted in 1991, ethylbenzene was classified as Group D (not classifiable as to human carcinogenicity) due to the lack of animal bioassays and human studies; however, the EPA assessment predated the NTP study. Ethyl-benzene is not included in the NTP's Report on Carcinogens; however, this may reflect that NTP has not recently considered the carcinogenicity of ethylbenzene, rather than a judgment that ethylbenzene is not carcinogenic.

Acute- and intermediate-duration studies provide strong evidence that ototoxicity is a sensitive effect following inhalation exposure to ethylbenzene. A more detailed discussion of this effect follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other effects.

A study of workers exposed occupationally to solvent mixtures that include ethylbenzene (mean exposure level 1.8 ppm) showed a 58% incidence of hearing loss compared to 36% in the reference (unexposed) group. The role of ethylbenzene in the observed losses cannot be ascertained from this study given that ethylbenzene was only one of several solvents, most of which were present at mean concentrations 1.5–3.5 times higher than ethylbenzene. Consistent with the outcome of occupational studies showing hearing loss, significant and persistent adverse auditory effects have been shown in animals after acute- and intermediate-duration inhalation exposures to ethylbenzene and after acute-duration oral exposures. OHCs in the organ of Corti (located in the cochlea) are a sensitive target of toxicity of ethylbenzene. Significant losses of OHCs in the organ or Corti were observed in male rats after acute-duration inhalation exposure to ≥400 ppm and intermediate-duration inhalation exposure to ≥200 ppm ethylbenzene. These losses in OHC were observed 8–11 weeks after the last exposures. Inhalation of ≥400 ppm ethylbenzene for 5 days or 4 weeks also resulted in a significant deterioration of auditory thresholds. The magnitude of the shifts in auditory thresholds observed after the first 4 weeks of exposure did not change during a 13-week exposure period or after an 8-week post-exposure recovery period. Inner hair cells were affected by ethylbenzene only at ≥600 ppm in the intermediate-duration study. Guinea pigs exposed to ethylbenzene at 2,500 ppm for 5 days did not show auditory deficits or losses in outer hair cells, whereas significant deficits and hair cell loss were observed in rats exposed to ethylbenzene at 550 ppm. An almost complete loss of OHC was reported in male rats 10 days after an acute-duration oral exposure to ethylbenzene. The mechanisms of the species differences between rats and guinea pigs are not understood. However, given the observations of hearing loss in workers exposed to 1.8 ppm ethylbenzene, the rat appears to be an appropriate animal model.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for ethylbenzene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on

noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

- An MRL of 10 ppm has been derived for acute-duration inhalation exposure (14 days or less) to ethylbenzene based on a NOAEL for significant deterioration in CAP auditory threshold and significant OHC loss at 400 ppm (LOAEL).

The database for acute-duration inhalation exposure to ethylbenzene is composed mostly of studies in laboratory animals. Some of the available reports and studies in humans are of limited use for dose-response assessment because insufficient information was provided to clearly characterize the exposure to ethylbenzene. Several studies with laboratory animals identify ototoxicity as the most sensitive end point for acute-duration inhalation exposure to ethylbenzene. Damage to the OHCs of the organ of Corti and, in some cases, significant reductions in auditory thresholds were observed in rats exposed to ≥400 ppm ethylbenzene by inhalation for 5 days (Cappaert et al. 1999, 2000, 2001, 2002). Losses of OHCs appeared to be concentration related as losses were 52–66% in animals exposed to 800 ppm ethylbenzene (Cappaert et al. 1999), 40–75% at 550 ppm, and approximately 25% at 400 ppm (Cappaert et al. 2000, 2001). OHC losses in rats exposed to 300 ppm were small (12%) and not statistically significant (Cappaert et al. 2000). Significant auditory deterioration, manifested as shifts in auditory thresholds, was also observed in rats exposed to ≥400 ppm ethylbenzene for 5 days (Cappaert et al. 1999, 2000, 2001, 2002). Auditory thresholds in rats exposed to ethylbenzene at ≥400 ppm were significantly affected in the mid-frequency region; however, an increasingly broader range of frequencies were affected with increasing concentrations of ethylbenzene (Cappaert et al. 1999, 2000). Cappaert et al. (2002) demonstrated a significant species difference in the susceptibility of rats and guinea pigs to the ototoxic effects of ethylbenzene with guinea pigs showing no auditory deficits or losses in OHCs at 2,500 ppm

ethylbenzene after 5 days (Cappaert et al. 2002). Auditory assessments indicate that effects were evident shortly after exposure and persisted for up to 11 weeks (termination of the observation period) (Cappaert et al. 1999, 2000, 2001, 2002). The data suggest that these auditory effects might be irreversible.

The observed damage to the auditory capacity of rats exposed to ethylbenzene during acute-duration studies reported in Cappaert et al. study (2000) was chosen as a critical effect to derive the acute-duration inhalation MRL. Ototoxicity was observed at relatively low exposure levels (400 ppm) and was a serious adverse effect that the impaired auditory threshold; no other adverse effects were observed at lower levels. An acute-duration MRL based on ototoxicity would be considered as protective of other effects observed in acute-exposure studies.

In the study by Cappaert et al. (2000), Wag/Rij rats (eight rats/group; sex not provided) were exposed to 0, 300, 400, or 550 ppm ethylbenzene (99% pure) 8 hours/day for 5 days. Animal weight was recorded weekly. Measurement of Distortion Product Otoacoustic Emissions (DPOAE), Compound Action Potential (CAP), and hair cell counts were conducted 3–6 weeks after the last ethylbenzene exposure. Exposed animals did not show clinical signs of intoxication and there were no significant differences in terminal body weight between exposed and control rats. DPOAE amplitude growth curves showed a significant reduction in rats exposed to 550 ppm, but not to 300 or 400 ppm ethylbenzene. Effects were significant at 5.6, 8, and 11.3 kHz, but not at other frequencies. The DPOAE thresholds were significantly shifted (increased stimulus was needed to elicit the threshold response) at 5.6, 8, 11.3, and 16 kHz in rats in the 550-ppm group. DPOAE threshold shifts were not observed in other exposure groups. Animals exposed to 550 ppm showed a significant shift in the CAP amplitude growth curves at 8, 12, and 16 kHz. In the 400-ppm group, the CAP growth curves were affected only at 12 kHz and there was no effect in animals in the 300-ppm group. CAP thresholds were significantly shifted at 8, 12, and 16 kHz in the 550-ppm group and at 12 and 16 kHz in the 400-ppm group. There was no deterioration of CAP thresholds in the 300-ppm group. Significant OHC losses of approximately 33 and 75% were observed in the 550-ppm group in the auditory regions corresponding to 11 and 21 kHz, respectively. In the 400-ppm group, significant losses (25%) were observed in the 11 kHz region. OHC losses in the 21 kHz region in the 300-ppm group were approximately 12%, but were not statistically significantly different from controls. This study identifies a NOAEL of 300 ppm and a LOAEL of 400 ppm for significant deterioration in CAP auditory thresholds and significant OHC losses.

A LOAEL/NOAEL approach was used to derive a point of departure to estimate an acute-duration inhalation MRL for ethylbenzene using the NOAEL of 300 ppm and the LOAEL of 400 ppm.

Application of a benchmark dose analysis was precluded because the results in Cappaert et al. (2000) were presented graphically and the details necessary to conduct a benchmark dose assessment, such as standard errors or standard deviations, were not clearly discernible. The NOAEL of 300 ppm was not adjusted for intermittent exposure given that the pharmacokinetics of ethylbenzene indicate that ethylbenzene will rapidly be absorbed, attain equilibrium with blood, be metabolized, and be eliminated from the body. Steady-state blood ethylbenzene concentrations achieved within 2 hours of initiating inhalation exposure to ethylbenzene concentration ranging from 75 to 500 ppm (Charest-Tardif et al. 2006). The blood elimination kinetics of inhaled ethylbenzene show that ethylbenzene is rapidly eliminated from the blood, with elimination half-times ranging from 3.3 to 63 minutes (e.g., nonlinearity of clearance with exposure concentration, similar elimination half-times (Charest-Tardif et al. 2006; Tardif et al. 1997). To calculate the human equivalent NOAEL ($NOAEL_{HEC}$), the NOAEL was multiplied by the ratio of the animal-to-human blood/gas partition coefficients for ethylbenzene. The blood/air partition coefficients for ethylbenzene were estimated to be 42.7 for the rat and 28.0 for the human (Tardif et al. 1997). Since the ethylbenzene blood/gas partitioning coefficient in animals is greater than the partitioning coefficient in humans, a default value of 1 is used for the animal-to-human blood/gas ratio (EPA 1994o). Thus, the $NOAEL_{HEC}$ is 300 ppm. The $NOAEL_{[HEC]}$ was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability), resulting in an acute-duration inhalation MRL of 10 ppm.

The developmental effects of inhaled ethylbenzene have been examined in high quality, guideline-compliant studies, which included complete examination of fetuses (Faber et al. 2006, 2007; NIOSH 1981; Saillenfait et al. 2003, 2006, 2007). Results of studies in rats indicate that ethylbenzene produces reduced fetal weight, skeletal anomalies, and delayed development of urogenital tract; skeletal anomalies and delayed urogenital development were observed in the presence of maternal toxicity (Faber et al. 2006; NIOSH 1981). Urogenital malformations (not specified) in mice and decreased fetal weight in rabbits also have been observed (Ungváry and Tátrai 1985); however, the usefulness of this study is hampered by the incomplete descriptions of the results and because an analysis of the results on a per litter basis was not provided. Malformations of the uropoietic apparatus at the ethylbenzene concentrations reported by Ungváry and Tátrai (1985) were not observed in longer-duration studies (Faber et al. 2006, 2007; Saillenfait et al. 2003, 2006, 2007).

Neurotoxic and respiratory effects were observed after acute-duration exposure to ethylbenzene at concentrations equal to or higher than those that elicited auditory effects in animals. Effects observed after acute-duration exposure to ethylbenzene include moderate activation of motor behavior in rats

exposed to 400 ppm (Molnar et al. 1986) and reduced activity and prostration and shallow breathing in rats and mice at 1,200 ppm (Ethylbenzene Producers Association 1986a). Rats or mice exposed to ≥2,000 ppm showed posture changes, reduced grip strength, reduced motor coordination (Tegeris and Balster 1994), narcotic effects (Molnar et al. 1986), and neurotransmission disturbances in the forebrain and hypothalamus (Andersson et al. 1981). Mice exposed to 4,060 ppm for 20 minutes showed a 50% reduction in respiratory rate (Nielsen and Alarie 1982). A 50% respiratory depression observed in mice at 1,432 ppm was attributed to sensory irritation (De Ceaurriz et al. 1981). Ethylbenzene concentrations of 1,000 ppm caused momentary ocular irritation, a burning sensation, and profuse lacrimation in humans (Thienes and Haley 1972; Yant et al. 1930). Male volunteers exposed to 2,000 ppm ethylbenzene reported throat irritation and chest constriction (Yant et al. 1930). No histopathological findings were made in the lungs of surviving rats, mice, or rabbits exposed to 1,200, 400, or 2,400 ppm ethylbenzene, respectively, for 4 days (Ethylbenzene Producers Association 1986a).

Increased liver weight was reported after acute-duration exposure in rats exposed to ≥400 ppm ethylbenzene (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). At these same levels and durations of exposures, induction of microsomal enzymes and related ultrastructural changes (e.g., proliferation of the smooth endoplasmic reticulum) were observed. These effects occurred in the absence of histopathological changes to the liver. Therefore, the effects on the liver appear to be related to induction of microsomal enzymes in smooth endoplamic reticulum.

Kidney weight was increased in rats exposed to ≥1,200 ppm (Ethylbenzene Producers Association 1986a; Toftgard and Nilsen 1982), but not in mice at 1,200 ppm or rabbits at 2,400 ppm (Ethylbenzene Producers Association 1986a). However, increased kidney weights occurred in the absence of histological changes (Ethylbenzene Producers Association 1986a).

- An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to ethylbenzene based on a loss of cochlear OHC at 200 ppm.

Otoxiticity (loss of cochlear OHC) observed in the study by Gagnaire et al. (2007) was selected as the critical effect to derive the intermediate-duration inhalation MRL. Ototoxicity was observed at relatively low exposure levels (200 ppm) and was a serious adverse effect that the impaired auditory threshold; no other adverse effects were observed at lower levels. An intermediate-duration MRL based on ototoxicity would be considered as protective of other effects observed in intermediate-exposure studies.

Male Sprague-Dawley rats (14 rats/exposure group) were exposed to 0, 200, 400, 600, and 800 ppm ethylbenzene (99% pure), 6 hours/day, 6 days/week, for 13 weeks (Gagnaire et al. 2007). Ototoxicity was assessed based on effects on neurophysiological measurements and cochlear total hair cell counts. Following the 8th week of recovery, eight rats/group were killed. In the 800-ppm group, one rat lost its head plug and could not undergo neurophysiological testing, one rat died for unknown reasons, and another rat was sacrificed due to a large neck tumor. There were no significant differences in body weight gain between the surviving treated animals and controls. Audiometric thresholds at 2, 4, 8, and 16 kHz were significantly higher than in animals exposed to 400, 600, and 800 ppm ethylbenzene in controls. The effect was evident at week 4, did not change throughout the exposure period, and was not reversed after 8 weeks of recovery. No shift in audiometric thresholds was observed in rats in the 200-ppm group; however, the morphological assessment of the organ of Corti showed significant losses (up to 30% of the outer hair cells in the mid frequency region) in the third row of the OHC in four of eight rats exposed to 200 ppm. A concentration-related loss in third row OHC (OHC3) was evident with almost complete loss observed in the 600- and 800-ppm groups. The data suggest that the extent of the damage at each concentration was greatest in the OHC3 followed, in decreasing order, by damage in OHC2, OHC1, and IHC. There was no significant hair cell loss in the control animals. The LOAEL for OHC3 loss was 200 ppm, the lowest concentration tested.

A LOAEL/NOAEL approach was used to derive a point of departure to estimate an intermediate-duration inhalation MRL for ethylbenzene. Application of a benchmark dose analysis was precluded because the results in the Gagnaire et al. (2007) study were presented graphically and the details necessary to conduct a benchmark dose assessment, such as standard errors or standard deviations, were not clearly discernible or, for those results where the necessary data were available, the benchmark models tested did not fit the data adequately.

The LOAEL of 200 ppm was not adjusted for intermittent exposure given that the pharmacokinetics of ethylbenzene indicate that ethylbenzene will rapidly be absorbed, attain equilibrium with blood, be metabolized, and be eliminated from the body. Steady-state blood ethylbenzene concentrations achieved within 2 hours of initiating inhalation exposure to ethylbenzene concentration ranging from 75 to 500 ppm (Charest-Tardif et al. 2006). The blood elimination kinetics of inhaled ethylbenzene show that ethylbenzene is rapidly eliminated from the blood, with elimination half-times ranging from 3.3 to 63 minutes (e.g., nonlinearity of clearance with exposure concentration, similar elimination half-times (Charest-Tardif et al. 2006; Tardif et al. 1997). To calculate the human equivalent LOAEL ($LOAEL_{HEC}$), the LOAEL is multiplied by the ratio of the animal-to-human blood/gas partition coefficients for

ethylbenzene. Since the ethylbenzene blood/gas partitioning coefficient in animals is greater than the partitioning coefficient in humans, a default value of 1 is used for the animal-to-human blood/gas ratio (EPA 1994o). Thus, the $LOAEL_{HEC}$ is 200 ppm. The $LOAEL_{HEC}$ was divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability) resulting in an intermediate-duration inhalation MRL of 0.7 ppm.

The database of toxicity studies of intermediate-duration inhalation exposures includes several studies in animals, but no studies in humans. The available animal studies indicate that rats are sensitive to the ototoxic effects of ethylbenzene (Gagnaire et al. 2007). This is in agreement with the results of acute-duration studies (Cappaert et al. 1999, 2000, 2001, 2002). Rats exposed to ≥400 ppm ethylbenzene via inhalation for 13 weeks showed significant increases in auditory thresholds after 4 weeks. These threshold shifts persisted unchanged for the duration of the exposure period and during an 8-week post-exposure recovery period (Gagnaire et al. 2007). Cell counts conducted in the organ of Corti after the 8-week recovery period showed significant losses of outer hair cells in rats exposed to ≥200 ppm. Concentration-related losses of inner hair cells (IHC) (14 and 32%) were observed in animals in the 600- and 800-ppm groups, respectively, with occasional IHC losses in the 400-ppm group. Exposed rats did not show clinical signs of toxicity or differences in body weight gain relative to unexposed animals (Gagnaire et al. 2007).

Systemic effects have been observed at concentrations equal to or higher than those that elicited ototoxic effects in rats. Increased liver, kidney, lung, and spleen weights have been observed in animals exposed to ethylbenzene concentrations in the 250- to 1,000-ppm range (Cragg et al. 1989; Elovaara et al. 1985; NIOSH 1981; NTP 1992; Wolf et al. 1956). For instance, significant increases in absolute and relative liver weights were observed in rats and mice exposed to 782 ppm for 4 weeks, but not in animals in the 382-ppm groups (Cragg et al. 1989). Liver weight was not affected in rabbits at concentrations as high as 1,610 ppm. No other organs, including lung or kidney, showed weight changes in rats or mice at 782 ppm or in rabbits at 1,610 ppm (Cragg et al. 1989). Gross and microscopic examination of over 30 organs (including organs of the respiratory, endocrine, digestive, renal, and nervous systems) did not show treatment-related effects in rats or mice exposed to 782 ppm or rabbits at 1,610 ppm (Cragg et al. 1989). Absolute and relative lung weights were significantly increased in female rats exposed to ≥250 ppm for 13 weeks; male rats showed an increased relative lung weight at 1,000 ppm (NTP 1992); however, there was no evidence of histopathological injury. Increased absolute and/or relative liver and kidney weights without evidence of histopathological injury were observed in male and female rats or mice exposed to ≥250 ppm ethylbenzene for 13 weeks (NTP 1992). Some of the organ weight increases

reported at the lower concentrations were <10% (NTP 1992) or deemed to be slight (Wolf et al. 1956). Neurological effects (sporadic salivation) were reported in rats at ≥382 ppm (Cragg et al. 1989). Cragg et al. (1989) observed small, but statistically significant, increases in platelet counts in male rats and leukocyte counts in female rats exposed to 782 ppm ethylbenzene for 4 weeks. Although no details were provided, Wolf et al. (1956) did not report hematological changes in animals exposed to up to 2,200 ppm.

Increased incidence of skeletal variations or all variations combined were observed in the offspring of pregnant rats exposed to ≥1,000 ppm ethylbenzene; however, on a per litter basis, significant increases were observed only at 2,000 ppm (Saillenfait et al. 2003). Fetal malformations in the offspring of rats exposed to ≤500 ppm ethylbenzene occurred at a low frequency and did not appear to be attributable to ethylbenzene exposure (Saillenfait et al. 2003, 2006, 2007). Significant reductions in fetal body weight were observed in the offspring of pregnant rats exposed to ≥1,000 ppm ethylbenzene during gestation (Saillenfait et al. 2003, 2006, 2007), but not in rats exposed to ≤500 ppm (Saillenfait et al. 2003, 2006, 2007). Maternal toxicity was observed only in rats exposed to ≥1,000 ppm as evidenced by the significant reduction in weight gain (corrected for gravid uterine weight) (Saillenfait et al. 2003, 2006, 2007). NIOSH (1981) observed an increase in the incidence of skeletal anomalies in the offspring of rats exposed to approximately 1,000 ppm during pre-mating and gestation. Increased maternal liver, kidney, and spleen weights were observed in that dose group. Developmental effects were not consistently evident at approximately 100 ppm. Developmental landmarks and neurodevelopment were not statistically or biologically significantly affected in the offspring of rats exposed to up to 500 ppm ethylbenzene in a two-generation reproductive toxicity test (Faber et al. 2006, 2007). Reproductive parameters were not significantly affected in animals exposed to ethylbenzene concentrations as high as 1,000 ppm (Saillenfait et al. 2003, 2006, 2007). Faber et al. (2006) reported a reduction in estrus cycle length in F0, but not F1, females exposed to 500 ppm ethylbenzene. There was no impairment in fertility or increased time to mating in the F0 females (Faber et al. 2006).

- An MRL of 0.3 ppm has been derived for chronic-duration inhalation exposure (365 days or more) to ethylbenzene based on a LOAEL of 75 ppm for nephropathy in rats.

In the NTP (1999) study, groups of F344/N rats (50 animals/sex/dose group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation 5 days/week, 6 hours/day, for 104 weeks. Animals were observed twice daily and clinical findings were recorded monthly. Body weights were recorded at the initiation of the study, weekly for the first 13 weeks, at week 16, monthly through the end of exposure, and prior to terminal necropsy. Animals that survived to study termination were killed by asphyxiation with CO_2. A complete necropsy and microscopic examination of major tissues and organs were performed on all rats

that survived to study termination or died early. Survival of male rats in the 750-ppm group was significantly less than that of the chamber controls. No clinical findings were attributed to ethylbenzene exposure. The severity of nephropathy observed in exposed rats was significantly increased in females at ≥75 ppm and in males at 750 ppm. In male rats exposed to 750 ppm, the incidences of renal tubule proliferative lesions were significantly increased relative to control animals. The incidences of renal tubule adenoma and adenoma or carcinoma (combined) in the 750-ppm group were significantly greater than the incidence in control animals. The incidence of renal tubule hyperplasia in 750 ppm males was significantly greater than that in the control group. An increase was observed in the incidence of cystic degeneration of the liver in male rats at 750 ppm.

In a 2-year study, female mice exposed to ≥250 ppm ethylbenzene showed an increased incidence of hyperplasia (characterized as focal, poorly delineated, monomorphic increases of cells lacking compressive features or altered arrangement) of the pituitary gland pars distalis relative to the incidence in control animals (NTP 1999). Male and female mice in the 750-ppm group showed an increased incidence of follicular cell hyperplasia in the thyroid gland. Eosinophilic foci of the liver were observed in females in the 750-ppm group at a higher incidence that in control animals. Syncytial alterations of hepatocytes were observed in male mice in all ethylbenzene exposure groups, but not in controls, with a significant increase in incidence observed at ≥250 ppm. Other nonneoplastic changes in male mice exposed to 750 ppm included mild-to-minimal hepatocellular hypertophy and hepatocyte necrosis (NTP 1999). The only available chronic-duration inhalation studies in animals suggest that a concentration-related increase in the severity of nephropathy in female rats is the most sensitive end point of ethylbenzene exposure. Thus, the study by NTP (1999) was selected to estimate a chronic-duration inhalation MRL.

A LOAEL/NOAEL approach was used to derive a point of departure to estimate a chronic-duration inhalation MRL for ethylbenzene. Application of a benchmark dose analysis was precluded because standard errors or standard deviations were not provided for the nephropathy severity ratings in the NTP (1999) study. The LOAEL of 75 ppm was not adjusted for intermittent exposure given that the pharmacokinetics of ethylbenzene indicate that ethylbenzene will rapidly be absorbed, attain equilibrium with blood, be metabolized, and be eliminated from the body. Steady-state blood ethylbenzene concentrations achieved within 2 hours of initiating inhalation exposure to ethylbenzene concentration ranging from 75 to 500 ppm (Charest-Tardif et al. 2006). The blood elimination kinetics of inhaled ethylbenzene show that ethylbenzene is rapidly eliminated from the blood, with elimination half-times ranging from 3.3 to 63 minutes (e.g., nonlinearity of clearance with exposure concentration, similar

elimination half-times (Charest-Tardif et al. 2006; Tardif et al. 1997). To calculate the human equivalent LOAEL ($LOAEL_{HEC}$), the LOAEL is multiplied by the ratio of the animal-to-human blood/gas partition coefficients for ethylbenzene. Since the ethylbenzene blood/gas partitioning coefficient in animals is greater than the partitioning coefficient in humans, a default value of 1 is used for the animal-to-human blood/gas ratio (EPA 1994o). Thus, the $LOAEL_{HEC}$ is 75 ppm. The $LOAEL_{HEC}$ was divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability) resulting in an intermediate-duration inhalation MRL of 0.3 ppm.

The database of chronic-duration inhalation studies with ethylbenzene includes a chronic-duration study in rats and mice (NTP 1999) and studies in humans. Hematological effects (increased average number of lymphocytes and decreased hemoglobin) were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985). Concentration-related increases in the severity of nephropathy were observed in female rats exposed to ≥75 ppm for 2 years (NTP 1999). In male rats, the severity of nephropathy was higher than in control animals only at 750 ppm (NTP 1999). Significant increases in the incidence of renal tubule hyperplasia were also observed in male and female rats in the 750-ppm groups.

Oral MRLs

Acute-duration Exposure. No studies describing acute-duration oral exposure of humans to ethylbenzene were found in the literature. Two animal studies have examined the acute oral toxicity of ethylbenzene. An almost complete loss of the three rows of OHCs in the organ of Corti were reported in male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks (Gagnaire and Langlais 2005). These losses were observed 10 days after the last dose. Although losses of OHCs have also been observed in acute-duration inhalation studies (Cappaert et al. 1999, 2000, 2001, 2002), Gagnaire and Langlais (2005) did not have a control group to establish the magnitude of the effects relative to unexposed animals. This study was used to rank the ototoxicity of 21 solvents administered by gavage. Nevertheless, the OHC losses observed in the ethylbenzene-treated animals were among the highest observed among the 21 organic solvents tested (Gagnaire and Langlais 2005). The 900 mg/kg/day dose was considered a serious LOAEL for ototoxicity. In the second study, doses of 500 or 1,000 mg/kg ethylbenzene decreased luteinizing hormone, progesterone, and 17 β-estradiol levels, increased stromal tissue with dense collagen bundles and reduced lumen in the uterus, and delayed the estrus cycle in female rats during the diestrus stage (Ungvary 1986). The poor reporting of the methods and results of the Ungvary (1986) study precludes using as the basis on an MRL.

Because the only dose tested in the Gagnaire and Langlais (2005) study is a serious LOAEL, an acute-duration oral MRL cannot be derived for ethylbenzene.

- An MRL of 0.5 mg/kg/day has been derived for intermediate-duration oral exposure to ethylbenzene based on the $BMDL_{10}$ of 48.2 mg/kg/day for hepatotoxicity (centrilobular hepatocyte hypertrophy) in male rats.

Hepatoxicity, specifically the incidence of centrilobular hepatocyte hypertrophy, was selected as the critical effect to derive the intermediate-duration oral MRL. Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, dose-related increased incidence of centrilobular hepatocyte hypertrophy, and the lack of evidence for adverse effects in other tissues or organ systems at lower oral intermediate-duration dosages, liver effects were selected as the basis for deriving the intermediate oral MRL. The critical study identified NOAEL and LOAEL values for hepatotoxicity of 75 and 250 mg/kg/day, respectively (Mellert et al. 2007). No other adverse effects were observed at lower doses.

In the principal study, groups of 10 male and 10 female Wister rats were administered ethylbenzene (no vehicle) by oral gavage at doses of 0, 75, 250, or 750 mg/kg/day for 13 weeks. The total daily dose of ethylbenzene was administered as split morning/evening half doses. Animals were examined daily for mortality and clinical signs. Food and water consumption and body weights were recorded weekly. A detailed clinical examination (ophthalmology and a functional observational battery [FOB]) and assessment of motor activity were conducted during the last week of treatment. After 13 weeks, urinalysis was conducted and blood samples were obtained and analyzed for hematology and clinical chemistry; organ weights were recorded and gross histopathologic examinations of the liver, kidney, and pancreas were conducted on animals in all groups. A comprehensive histopathological examination of tissues was performed in the control and 750 mg/kg/day groups.

No mortalities were observed during the course of the study (Mellert et al. 2007). Clinical signs (post-dosing salivation) in treated animals were observed in all animals administered ≥250 mg/kg/day and in one animal administered 75 mg/kg/day. Terminal body weight in males was significantly decreased by 14% compared to controls in the 750 mg/kg/day group. Mean corpuscular volume was increased in males and females and platelet count was reduced in females treated with 750 mg/kg/day. Prothrombin time was significantly decreased (<8% compared to controls) in females administered ≥250 mg/kg/kg, but no changes in prothrombin times were observed in males in any treatment group. Effects indicative of liver

toxicity included increased activity of serum liver enzymes ALT and GGT in males (≥250 mg/kg/day) and females (750 mg/mg/day), increased absolute and relative liver weights (≥250 mg/kg/day in males and females), and a dose-related increase in the incidence of centrilobular hepatocyte hypertrophy (≥250 mg/kg/day in males and females). Increased bilirubin (≤250 mg/kg/day in males and 750 mg/kg/day in females), total protein (750 mg/kg/day in females), albumin (750 mg/kg/day in males and females), globulins (750 mg/kg/day in females), and cholesterol (≤250 mg/kg/day in males and females), and decreased prothrombin time (750 mg/kg/day in males and ≥250 mg/kg/day in females) were considered by study investigators as adaptive effects in the liver. In males in the 75 mg/k/day group, relative liver weight was significantly increased by (4% compared to controls); however, no histopathological changes or increases in absolute liver or serum liver enzyme activities were observed at this dosage. Given that ethylbenzene is a microsomal enzyme inducer and the absence of histopathology and other evidence of liver injury at the 75 mg/kg/day dosage, the small increase in relative liver weight in male rats at this dosage was not considered indicative of an adverse effect on the liver.

Renal effects in males included increased serum creatinine (750 mg/kg/day), increased incidences of transitional epithelial cells and granular and epithelial cell casts in the urine (≥250 mg/kg/day), increased absolute and relative kidney weights (≥250 mg/kg/day), and a dose-related increase in severity of hyaline droplet nephropathy (≥250 mg/kg/day) (Mellert et al. 2007). Adverse renal effects in males were most likely related to accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Absolute kidney weight was significantly increased by 7 and 13% in females administered 250 and 750 mg/kg/day, respectively, compared to controls. However, since no histopathological findings or alterations in urinalysis parameters were observed, increased kidney weight in females was not considered adverse. Absolute and relative thymus weights were decreased in females treated with ≥250 mg/kg/day, but no histopathological findings were observed. Histopathological examination of all other tissues did not reveal any abnormalities. Results of the FOB did not reveal consistent treatment-related effects. NOAEL and LOAEL values of 250 and 750 mg/kg/day, respectively, were identified based on hepatotoxicity in male and female rats.

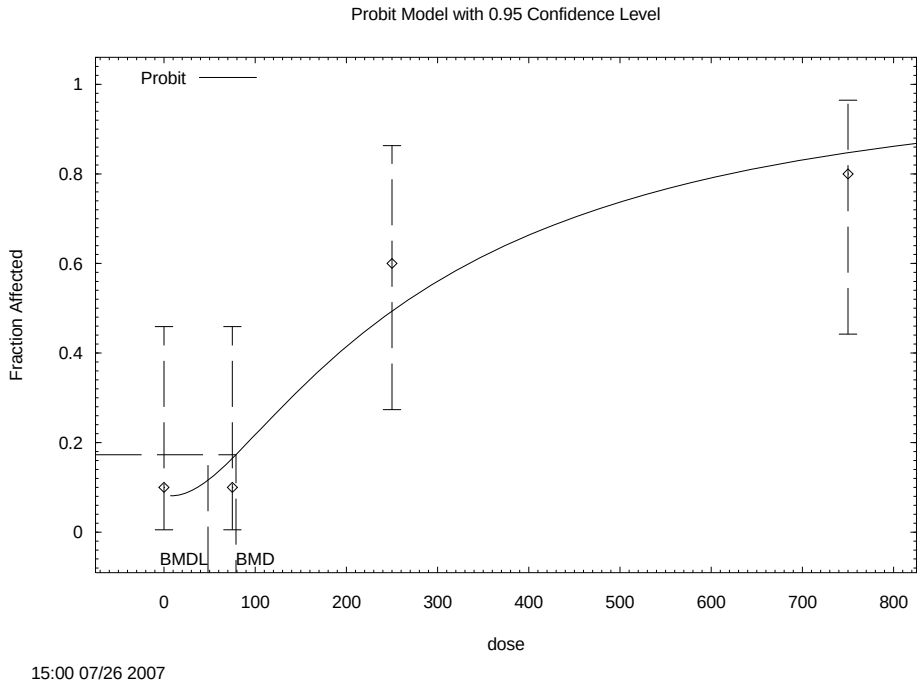
Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, and incidence of centrilobular hepatocyte hypertrophy), the liver was identified as the most sensitive target for oral ethylbenzene, with NOAEL and LOAEL values of 75 and 250 mg/kg/day, respectively. Since serum liver enzyme activities were increased in the mid- and high-dose groups in males, but only in the high-dose group in females, males appeared more sensitive than females to hepatic effects of oral ethylbenzene. To determine the point of departure for derivation of the intermediate-

duration MRL, data sets for serum liver enzymes (ALT and GGT), relative liver weight, and centrilobular hepatocyte hypertrophy in male rats were evaluated for suitability for benchmark dose (BMD) modeling. Using all available continuous variable models in the EPA Benchmark Dose Software (BMDS) version 1.3.2 (EPA 2000), no models provided adequate fit to the data for serum liver enzymes and relative liver weights; therefore, these data sets were considered unsuitable for BMD analysis. Data for the incidence of centrilobular hepatocyte hypertrophy were analyzed using all available dichotomous models in the EPA Benchmark Dose Software (version 1.3.2). Predicted doses associated with a 10% extra risk were calculated. As assessed by the chi-square goodness-of-fit statistic, all available dichotomous models provided adequate fit (X^2 p>0.1). Comparing across models, a better fit is generally indicated by a lower Akaike's Information Criteria (AIC). As assessed by AIC, the log-probit model (Figure 2-1) provided the best fit to the data. The BMD_{10} and $BMDL_{10}$ predicted by the log-probit model for the data on centrilobular hepatocyte hypertrophy in male rats were 78.9 and 48.2 mg/kg/day, respectively. The $BMDL_{10}$ of 48.2 mg/kg/day for male rats was selected as the point of departure for deriving the intermediate-duration oral MRL.

The $BMDL_{10}$ of 48.2 mg/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an intermediate-duration oral MRL of 0.5 mg/kg/day.

The intermediate-duration oral database for ethylbenzene is limited to the critical study by Mellert et al. (2007) evaluating the effects of oral exposure of rats to ethylbenzene for 4 and 13 weeks, and a poorly reported 6-month exposure study in rats (Wolf et al. 1956). Results of the 4-week exposure study in rats are similar to those observed in the 13-week study, showing that the liver is the primary target organ for oral ethylbenzene. Effects consistent with hepatotoxicity include increased absolute and relative liver weights (≥250 mg/kg/day in males and 750 mg/kg/day in females), increased incidence of hepatocyte centrilobular (≥250 mg/kg/day in males and 750 mg/kg/day in females), and increased serum liver enzyme activity (ALT) (750 mg/kg/day in males and females). The increase in relative kidney weight and hyaline droplet nephropathy in males administered ≥250 mg/kg/day was most likely secondary to increases accumulation of accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. The 4-week study identified NOAEL and LOAEL values of 250 and 750 mg/kg/day, respectively, for liver in male rats (Mellert et al. 2007). Histopathological changes characterized by cloudy swelling of parenchymal cells of the liver and an increase in liver weight were observed in female rats administered 408 mg/kg/day by gavage for 6 months (Wolf et al. 1956). No other hepatic changes

Figure 2-1. Predicted (Log-Probit Model) and Observed Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to Oral Ethylbenzene by Gavage for 13 Weeks*



*BMDs and BMDLs indicated are associated with a 10% extra risk change from the control, and are in units of mg/kg/day.

were reported. No liver effects were observed in female rats administered 136 mg/kg/day. However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

Although no additional data are available regarding the effects of intermediate oral exposure to ethylbenzene, results of an acute-duration oral study indicate that ethylbenzene is ototoxic (Gagnaire and Langlais 2005). In male rats administered 900 mg/kg/day (the only dose tested) by gavage for 2 weeks, an almost complete loss of the three rows of OHCs in the organ of Corti was observed in male rats (Gagnaire and Langlais 2005). The 4- and 13-week oral studies by Mellert et al. (2007) did not examine the cochlea or measure auditory function. Therefore, it is not possible to determine whether ototoxicity occurred in the 4- and 13-week studies.

Chronic-duration Exposure. No studies describing the non-carcinogenic effects of chronic-duration oral exposure to ethylbenzene in humans or animals were located.