APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: August 2007
Profile Status: Final Pre-Public Draft
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 10 [ ] mg/kg/day [x] ppm

Reference: Cappaert NLM, Klis SFL, Baretta AB, et al. 2000. Ethyl benzene-induced ototoxicity in rats: A dose-dependent mid-frequency hearing loss. J Assoc Res Otolaryngol 1(4):292-299.

Experimental design: 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.
DPOAE: Stimuli were delivered to the ear canal via a probe system incorporating two speakers and a low-noise microphone. The microphone signal was amplified and the response to the stimulus was measured. DPOAE amplitude growth curves with stimulus levels were obtained from both ears. Growth functions were obtained at 4, 5.6, 8, 11.3, 16, and 22.6 kHz. The DPOAE threshold, defined as the stimulus level required to elicit a response of 0 dB SPL DPOAE was determined for each of the six frequencies.
CAP: CAP was conducted immediately after DPOAE measurements. Auditory-evoked responses were recorded via a silverball electrode at the apex of the cochlea after presenting tone bursts of 1, 2, 4, 8, 12, 16, and 24 kHz. An isoresponsive criterion of 1 µV level was used to define CAP thresholds. CAP amplitude was defined as the difference between the first negative peak and the summating potential in the electrophysiologic response. Hair cell counts: Immediately after conducting the electrocochleography (CAP) cochleas were removed and bisected longitudinally. Hair cell counts were conducted on five locations of the organ of Corti. Outer hair cell (OHC) loss was determined and expresses as a percentage of the expected number of OHC in different auditory regions.

Effect noted in study and corresponding doses: Rats did not show signs of ill health. There were no significant differences in terminal body weight between exposed and control rats.
DPOAE: DPOAE amplitude growth curves showed a significant reduction in rats exposed to 550 ppm, but not 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.
CAP: 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 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 significant.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 300 ppm and a LOAEL of 400 ppm for significant deterioration in CAP auditory thresholds and significant OHC losses.

[x] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent concentration (HEC) for the NOAEL was calculated using Formula 4-48 (page 4-60), from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994o). The recommended equation is that for category 3 gases:

$$\text{NOAEL}_{[\text{HEC}]}\,(\text{ppm}) = \text{NOAEL}_{[\text{ADJ}]}\,(\text{ppm}) \times \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 300 \text{ ppm} \times [1] = 300 \text{ ppm}$$

where:

$(H_{b/g})_A$, $(H_{b/g})_H$ = Blood/gas partition coefficient in animal and human blood, respectively. Blood/gas partition coefficients of 30.2 and 28.2 for rat and human blood, respectively, were obtained (Abraham et al. 2005). However, when $(H_{b/g})_A > (H_{b/g})_H$, a value of 1 is used for the ratio (EPA 1994o). Thus, a default value of 1.0 was used for the animal-to-human blood gas ratio.

Was a conversion used from intermittent to continuous exposure? No adjustment for intermittent exposure was made because 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).

Other additional studies or pertinent information that lend support to this MRL: Cappaert et al. (1999, 2001, 2002) showed significant adverse effects in the auditory system of rats after acute-duration exposures to ≥400 ppm ethylbenzene via inhalation. OHC losses, generally the most sensitive end point evaluated in these studies, showed a concentration-related pattern. Functional auditory deficits were observed at exposure concentrations that were greater than or equal to the concentrations that elicited OHC loss. Rats administered ethylbenzene by gavage at 8.47 mmol/kg/day (900 mg/kg/day), 5 days/week for 2 weeks showed almost complete loss of the three rows of OHCs (Gagnaire and Langlais 2005). An intermediate-duration study in rats showed significant irreversible ototoxicity in rats exposed to ≥200 ppm ethylbenzene via inhalation.

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: August 2007
Profile Status: Final Pre-Public Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 40
Species: Rat

Minimal Risk Level: 0.7 [ ] mg/kg/day [x] ppm

Reference: Gagnaire F, Langlais C, Grossman S, et al. 2007. Ototoxicity in rats exposed to ethylbenzene and to two xylene vapors for 13 weeks. Arch Toxicol 81:127-143.

Experimental design: 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. Ototoxicity was assessed based on effects on neurophysiological measurements and cochlear total hair cell counts. For the neurophysiologic assessments, rats were surgically fitted with electrodes (active electrode was placed at the lamba point over the inferior colliculus, the reference electrode was placed posterior to the bregma and to the right of the midline, and the ground electrode was placed over the nasal bone). Exposure to ethylbenzene was conducted starting 3–4 weeks after implantation of the electrodes and neuro-physiological measurements were conducted at the end of 4^{th}, 8^{th}, and 13^{th} week of exposure and at the end of the 8^{th} week of recovery (week 21). Brainstem auditory responses were evoked with 50 microsecond clicks at 10 clicks/second presented in 5 dB steps. The evoked activity was analyzed for 10 ms following each click. Audiometric thresholds were determined at 2, 4, 8, and 16 kHz by inspection of the auditory brainstem responses. Following the 8^{th} week of recovery (post-exposure) eight rats/group were sacrified. The organ of Corti and the basilar membrane were dissected from the cochlea and prepared for total hair cell counts (cytocochleograms). Four left and four right cochleas were prepared in this manner in all groups including controls.

Effect noted in study and corresponding doses: 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 in animals exposed to 400, 600, and 800 ppm ethylbenzene than in controls ($p<0.05$). The effect was evident at week 4, did not increase significantly 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.

The morphological assessment of the organ of Corti (conducted after an 8-week recovery period) showed significant losses (up to 30% of the OHC in the mid frequency region) in the third row of the OHC in 4/8 rats exposed to 200 ppm. A dose 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 dose was greatest in the OHC3 followed, in decreasing order, by damage in OHC2, OHC1, and inner hair cells (IHC). There was no significant hair loss in the control animals. The LOAEL for OHC3 loss was 200 ppm. A NOAEL was not established.

Dose and end point used for MRL derivation: The MRL is based on a LOAEL of 200 ppm for significant loss of cochlear OHCs after 13 weeks of exposure.

[ ] NOAEL [x] LOAEL

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: The human equivalent concentration (HEC) for the LOAEL was calculated using Formula 4-48 (page 4-60), from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994o). The recommended equation is that for category 3 gases:

$$\text{LOAEL}_{[\text{HEC}]}\,(\text{ppm}) = \text{LOAEL}_{[\text{ADJ}]}\,(\text{ppm}) \times \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 200\ \text{ppm} \times [1] = 200\ \text{ppm}$$

where:

$(H_{b/g})_A$, $(H_{b/g})_H$ = Blood/gas partition coefficient in animal and human blood, respectively. Blood/gas partition coefficients of 30.2 and 28.2 for rat and human blood, respectively, were obtained (Abraham et al. 2005). However, when $(H_{b/g})_A > (H_{b/g})_H$, a value of 1 is used for the ratio (EPA 1994o). Thus, a default value of 1.0 was used for the animal-to-human blood gas ratio.

Was a conversion used from intermittent to continuous exposure? No adjustment for intermittent exposure was made because 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).

Other additional studies or pertinent information that lend support to this MRL: Significant adverse effects on the auditory system was observed in rats after acute-duration exposures to ≥400 ppm ethylbenzene via inhalation (Cappaert et al. 1999, 2000, 2001, 2002). OHC losses, usually the most sensitive end point evaluated in these acute-duration studies, showed a concentration-related pattern. Functional auditory deficits were observed at exposure concentrations that were greater than or equal to the concentrations that elicited OHC loss. Rats administered ethylbenzene by gavage at 8.47 mmol/kg/day (900 mg/kg/day), 5 days/week for 2 weeks showed almost complete loss of the three rows of OHCs (Gagnaire and Langlais 2005).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: August 2007
Profile Status: Final Pre-Public Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 60
Species: Rat

Minimal Risk Level: 0.3 [ ] mg/kg/day [x] ppm

Reference: NTP. 1999. NTP technical report on the toxicology and carcinogenesis studies of ethylbenzene in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services. NTP TR 466.

Experimental design: Groups of F344/N rats and B6C3Fl mice (50 animals/sex/dose group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation for 5 days/week, 6 hours/day, for 104 (rats) or 103 (mice) 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 were performed on all rats and mice that survived to study termination or died early. The tissues examined included the adrenal gland, blood vessel (aorta), bone and marrow, brain, clitoral gland, esophagus, gall bladder, harderian gland, heart, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

Effect noted in study and corresponding doses: Survival of male rats in the 750-ppm group was significantly less than that of control animals. Survival was not affected in rats in other exposure groups or in mice at any ethylbenzene concentration. No clinical findings were attributed to ethylbenzene exposure in rats or mice. The severity of nephropathy observed in exposed rats was significantly increased in females at ≥75 ppm and in males at 750 ppm. Nephropathy was characterized by dilation of renal tubules with hyaline or cellular casts, interstitial fibrosis, infiltration of inflammatory cells, tubular regeneration, and transitional hyperplasia of the renal papilla. 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. Significant increases were observed in the incidence of interstitial cell adenoma and bilateral testicular adenoma in males in the 750-ppm group. An increase was observed in the incidence of cystic degeneration of the liver in male rats at 750 ppm. Significant increases in the incidence of hyperplasia of the pituitary gland pars distalis were observed in female mice at ≥250 ppm. A significant increase in the incidence of alveolar epithelial metaplasia was observed in male mice in the 750-ppm group. In 750-ppm males, the incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly greater than those in control animals but remained within the historical control ranges. The incidence of hepatocellular adenoma and adenoma or carcinoma (combined) in female mice was

significantly increased in the 750-ppm group. 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 hypertrophy and hepatocyte necrosis. A significant increase in incidences of follicular cell hyperplasia was observed in male and female mice in the 750-ppm groups.

A NOAEL was not established.

Dose and end point used for MRL derivation: The MRL is based on a LOAEL of 75 ppm for significant increases in the severity of nephropathy in female rats after 2 years of exposure.

[ ] NOAEL [x] LOAEL

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustment
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: The human equivalent concentration (HEC) for the LOAEL was calculated using Formula 4-48 (page 4-60), from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994o). The recommended equation is that for category 3 gases:

$$\text{LOAEL}_{[\text{HEC}]}\,(\text{ppm}) = \text{LOAEL}_{[\text{ADJ}]}\,(\text{ppm}) \times \frac{(H_{b/g})_A}{(H_{b/g})_H}$$

$$= 75\ \text{ppm} \times [1] = 75\ \text{ppm}$$

where:

$(H_{b/g})_A$, $(H_{b/g})_H$ = Blood/gas partition coefficient in animal and human blood, respectively. Blood/gas partition coefficients of 30.2 and 28.2 for rat and human blood, respectively, were obtained (Abraham et al. 2005). However, when $(H_{b/g})_A > (H_{b/g})_H$, a value of 1 is used for the ratio (EPA 1994o). Thus, a default value of 1.0 was used for the animal-to-human blood gas ratio.

Was a conversion used from intermittent to continuous exposure? No adjustment for intermittent exposure was made because the pharmacokinetics of ethylbenzene indicate that ethylbenzene will rapidly be absorbed, attain equilibrium with blood, be metabolized, and 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).

Other additional studies or pertinent information that lend support to this MRL: A limited number of studies have examined the chronic toxicity of ethylbenzene. Two studies have looked at possible effects in workers chronically exposed to ethylbenzene and NTP (1999) examined chronic toxicity in rats and

mice. Hematological effects (increased average number of lymphocytes and decreased hemoglobin) were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985). No hematological effects, liver lesions or effects on liver function were reported in a study of workers exposed chronically (>20 years) to ethylbenzene (Bardodej and Cirek 1988). Exposure levels were not indicated in the latter study, but the risk of ethylbenzene exposure in this production plant was reported as negligible. An increased incidence of hyperplasia of the pituitary gland pars distalis was observed in female mice exposed to 250 ppm (NTP 1999). At 750 ppm, increased incidence of follicular cell hyperplasia in the thyroid gland and syncytial alterations of the hepatocytes, hypertrophy, and hepatic necrosis were observed in mice (NTP 1999).

Agency Contacts (Chemical Managers): Jessilynn Taylor, Henry Abadin, Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: August 2007
Profile Status: Final Pre-Public Draft
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.5 [x] mg/kg/day [ ] ppm

Reference: Mellert W, Deckardt K, Kauffmann W, et al. 2007. Ethylbenzene: 4- and 13-week rat oral toxicity. Arch Toxicol 81:361-370.

Experimental design: 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.

Effect noted in study and corresponding doses: 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. 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). Adverse renal effects in males were most likely related to accumulation of α2μ-globulin, 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, the increased kidney weight in females was not considered indicative of an adverse kidney effect in female rats. Absolute and relative thymus weights were decreased in females treated with ≥250 mg/kg/day, but no histopathological findings were observed. Results of the FOB did not reveal consistent treatment-related effects.

Dose and end point used for MRL derivation: Based on evidence of hepatotoxicity (increased serum liver enzyme activity, absolute and relative liver weights, and 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, 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 the adverse 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 (Table A-1) 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) (Table A-2). 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 A-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.

[ ] NOAEL [ ] LOAEL [X] BMDL

Table A-1. Incidence Data for Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to Ethylbenzene for 13 Weeks

Dose group (mg/kg/day)	Incidence
0	1/10
75	1/10
250	6/10
750	8/10

Source: Mellert et al. 2007

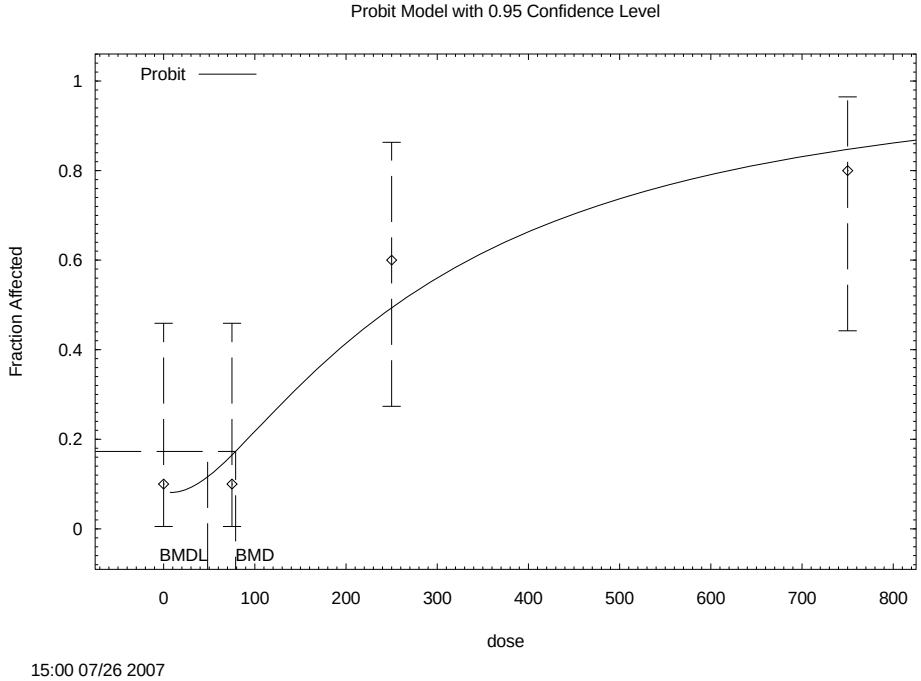
Table A-2. Modeling Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to Oral Ethylbenzene by Gavage for 13 Weeks

Model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg /kg/day)	x^2 *p*-value	AIC
Gamma[a]	61.5899	29.1257	1.60	44.152
Logistic	114.336	73.5251	3.46	43.9535
Log-logistic[b]	73.0775	18.2396	1.04	43.5549
Multi-stage[c]	46.8785	28.9177	1.62	42.2384
Probit	112.022	76.3196	3.44	43.9119
Log-probit[b]	**78.9472**	**48.2564**	**0.98**	**41.482**
Quantal linear	46.8785	28.9177	1.62	42.2384
Quantal quadratic	173.773	126.831	4.80	44.9624
Weibull[a]	54.5432	28.9959	1.62	44.2057

[a]Restrict power ≥1.
[b]Slope restricted to >1.
[c]Restrict betas ≥0; lowest degree polynomial with an adequate fit is reported; degree of polynomial=3.

Source: Mellert et al. 2007

Figure A-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.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a less serious LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The selection of $BMDL_{10}$ of 48.2 mg/kg/day, derived for male rats exposed to ethylbenzene for 13 weeks (Mellert et al. 2007), as a point of departure for deriving an intermediate-duration oral MRL for ethylbenzene is supported by results a 4-week oral gavage study in rats (Mellert et al. 2007) and a 6-month oral study in rats (Wolf et al. 1956). Results of the 4-week gavage study in rats were similar to those of the 13-week study, identifying NOAEL and 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 increased 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 (Wolf et al. 1956). No other hepatic changes were reported. No liver effects were observed in female rats administered 136 mg/kg/day (Wolf et al. 1956). However, this study was poorly reported and did not provide adequate descriptions of study methods or results.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

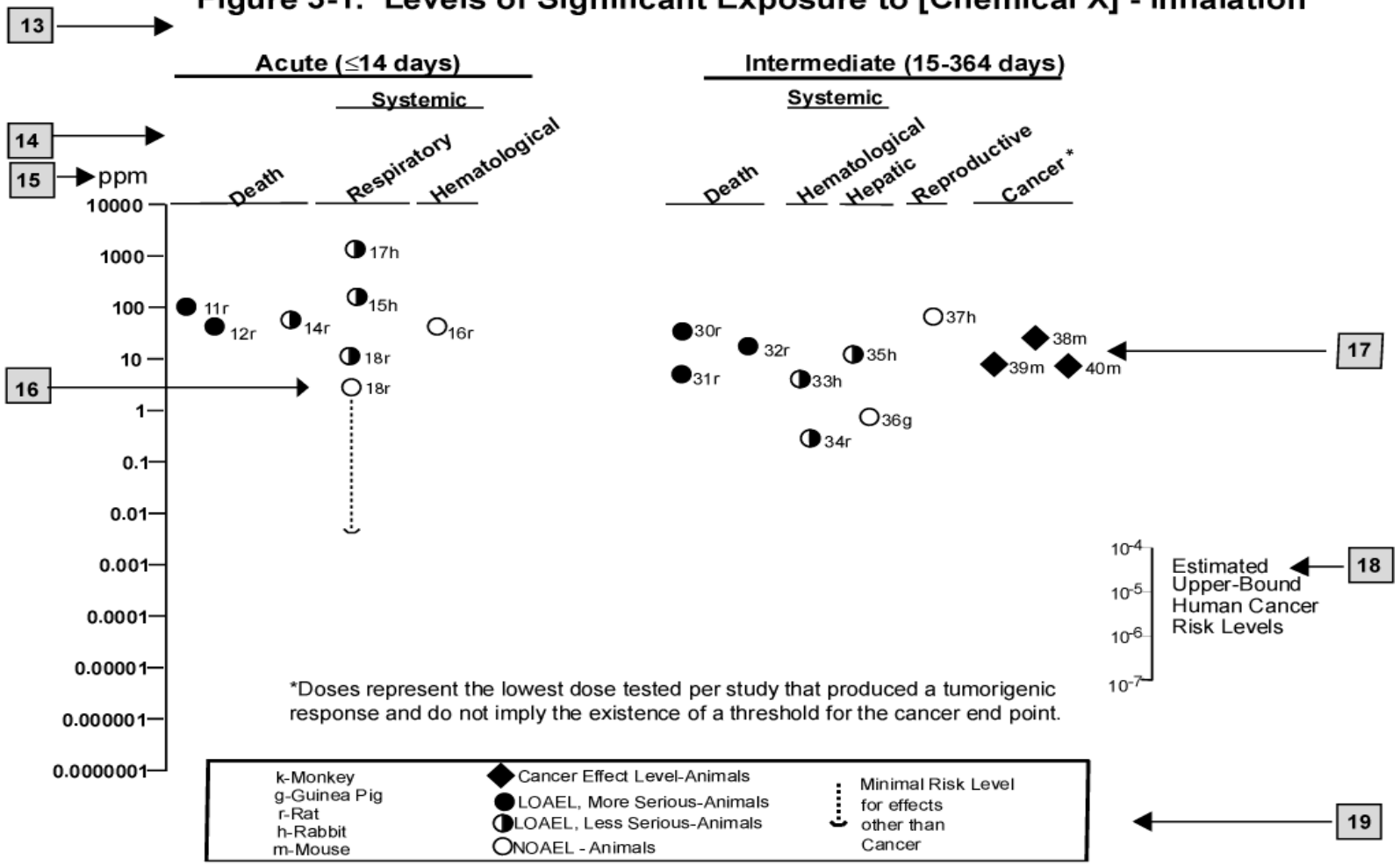
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX