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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-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 5 [ ] 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 (8 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: $BMCL_{1SD}$ of 81.10 µmol/L for CAP auditory shifts using an internal dose metric of time-averaged arterial blood concentration of ethylbenzene.

[] NOAEL [ ] LOAEL [x] BMCL

The point of departure for an acute-duration inhalation MRL was identified using BMD analysis of the CAP auditory threshold data from the Cappaert et al. (2000) study. The data were presented graphically in the paper; however, Dr. Cappaert provided individual animal data for the CAP thresholds (presented in Figures 3 and 4 in the published paper) to ATSDR (data on OHC loss were not available). Data from Figure 4 included measurements of CAP thresholds in response to auditory stimuli ranging from 1 to 24 kHz. The largest effects on CAP threshold occurred in response to 8, 12, and 16 kHz stimuli and, on this basis, these data were selected for BMD modeling. The raw data set from Dr. Cappaert was used to make the following calculations:

1. *Control group mean (±SD) CAP threshold*: mean CAP stimulus threshold (dB SPL, defined as ≥1 µV CAP) of control group;

2. *Individual animal threshold shift in response to ethylbenzene exposure*: mifference between threshold for each animal exposed to ethylbenzene and the control group mean threshold; and

3. *Ethylbenzene exposure group mean (±SD) threshold shift*: mean (±SD) of individual threshold shifts for each ethylbenzene exposure group. These group mean responses (mean CAP threshold shift, dB) were used as the response metric in BMD modeling.

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001) (see Appendix E for additional information on the PBPK model). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. For cochlear effects, the assumption was made that ethylbenzene, rather than a metabolite, is the toxic agent. Although there are no data for ethylbenzene, support of this assumption comes from studies of toluene (Pryor et al. 1991) and styrene (Ladefoged et al. 1998), which found that ototoxicity was most likely due to the action of the parent compound rather than a metabolite. The dose metric simulated for the cochlear effects was time-averaged arterial blood concentration of ethylbenzene (MCA) because there are no validated models for simulating ethylbenzene levels in cochlea tissue or enodolymph. Using MCA for this end point assumes that tissue dosimetry and response would be correlated with time averaged arterial ethylbenzene concentrations (or average x time, AUC), which would be expected to correlate with time-averaged tissue concentration.

The CAP threshold shift data (summarized in Table A-1) were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.1.1) using MCA as the dose metric. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual

at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. If the test for constant variance was negative, then the linear model was run again while applying the power model integrated into BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all models, a BMR of 1 standard deviation change from the control was used. This default BMR was used because there are insufficient mechanism of action data to determine what level of response constitutes a biologically significant effect in the cochlea.

Table A-1. CAP Threshold Shifts in Wag/Rij Rats Exposed to Ethylbenzene 8 Hours/Day for 5 Days

Frequency (kHz)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB)	SD	Number of rats
8					
	0	0	0.00	5.66	7
	300	76.11	-3.45	11.09	8
	400	119.00	4.36	9.94	7
	550	198.10	23.93	6.11	8
12					
	0	0	0.00	6.30	7
	300	76.11	-3.51	11.31	8
	400	119.00	14.79	9.53	7
	550	198.10	30.62	5.78	8
16					
	0	0	0.00	7.18	7
	300	76.11	-0.35	10.43	8
	400	119.00	15.57	12.00	7
	550	198.10	21.84	7.37	8

CAP = compound action potential; MCA = time-averaged arterial blood concentration of ethylbenzene; SD = standard deviation

Source: Cappaert et al. 2000

The model predictions for CAP threshold shifts at 8, 12, and 16 kHz are summarized in Table A-2. At the 8 kHz frequency, the Hill, polynomial (2- and 3-degree), and power models provided adequate fit to the data. Of these models, the polynomial (3-degree) model (Figure A-1) had the lowest AIC. At 12 and 16 kHz frequencies, only the Hill model provided an adequate fit to the data; the models are presented in Figures A-2 and A-3.

Table A-2. Model Predictions for CAP Threshold Shifts in Wag/Rij Rats Exposed to Ethylbenzene 8 Hours/Day for 5 Days

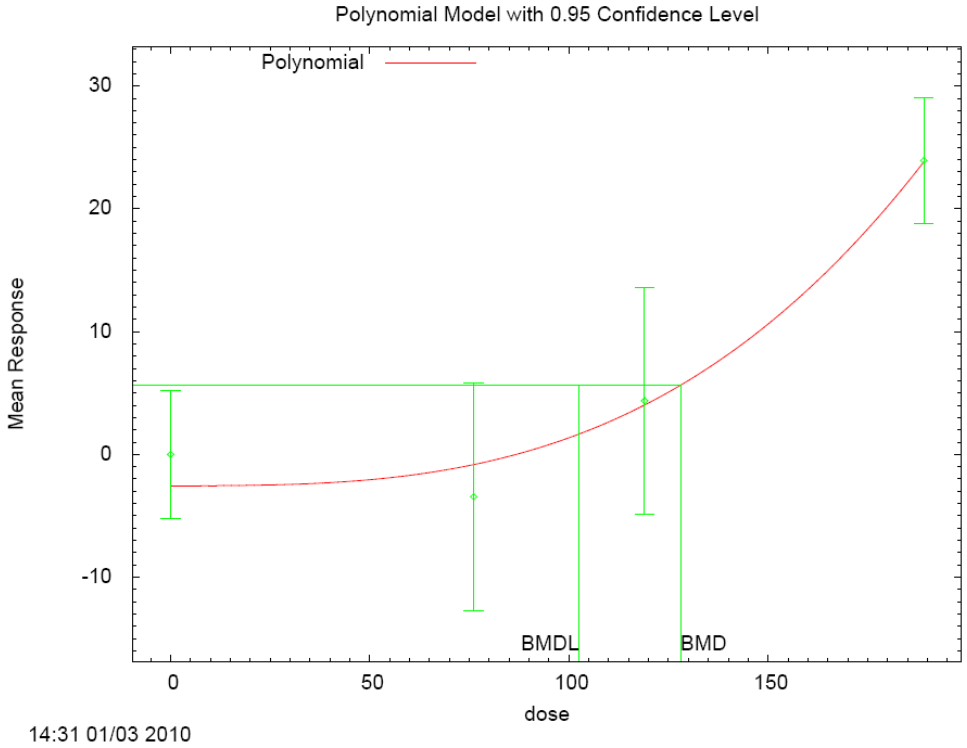
Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
8 kHz frequency					
Constant variance					
Hill[b]	0.17	0.41	163.26	121.43	104.55
Linear[c]	0.17	0.00	174.14	NA	NA
Polynomial (2-degree)[b]	0.17	0.14	164.53	105.93	91.96
Polynomial (3-degree)[b]	**0.17**	**0.46**	**162.12**	**128.00**	**102.63**
Power[b]	0.17	0.24	163.94	136.36	101.61
12 kHz frequency					
Constant variance					
Hill[b]	**0.19**	**0.40**	**163.36**	**111.59**	**89.47**
Linear[c]	0.19	0.00	176.02	NA	NA
Polynomial (2-degree)[b]	0.19	0.03	167.42	NA	NA
Polynomial (3-degree)[b]	0.19	0.01	169.42	NA	NA
Power[b]	0.19	0.01	169.32	NA	NA
16 kHz frequency					
Constant variance					
Hill[b]	**0.42**	**0.94**	**168.39**	**110.51**	**81.10**
Linear[c]	0.42	0.04	172.72	NA	NA
Polynomial (2-degree)[b]	0.42	0.03	173.35	NA	NA
Polynomial (3-degree)[b]	0.42	0.03	173.35	NA	NA
Power[b]	0.42	0.03	173.12	NA	NA

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a 1 standard deviation benchmark response; BMCL = 95% lower confidence limit on the BMC; CAP = compound action potential; NA = not applicable, model does not provide adequate fit to the data

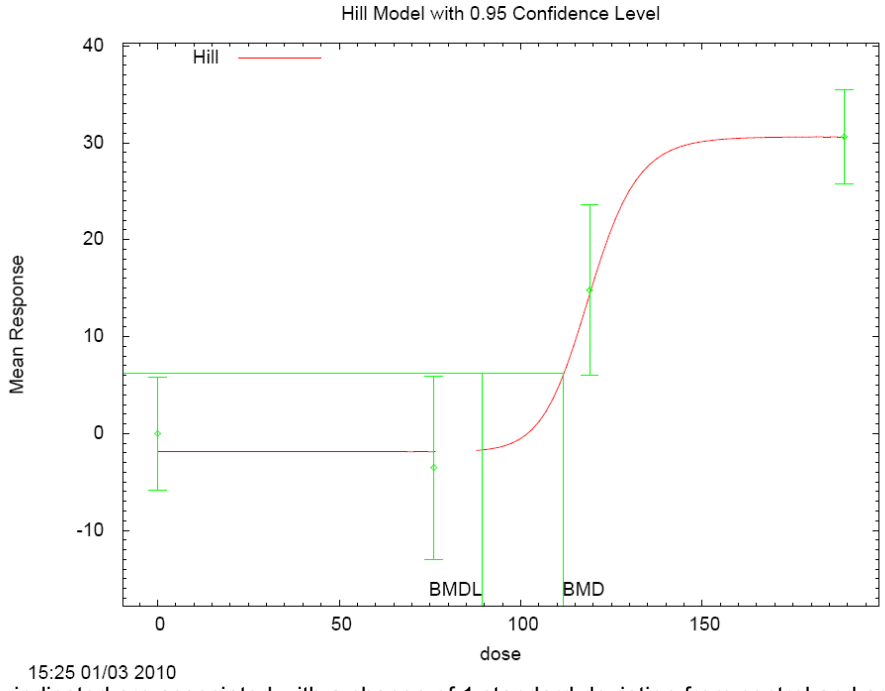
Source: Cappaert et al. 2000

Figure A-1. Predicted (3-Degree Polynomial Model with Constant Variance) and Observed CAP Threshold Shifts at 8 kHz *



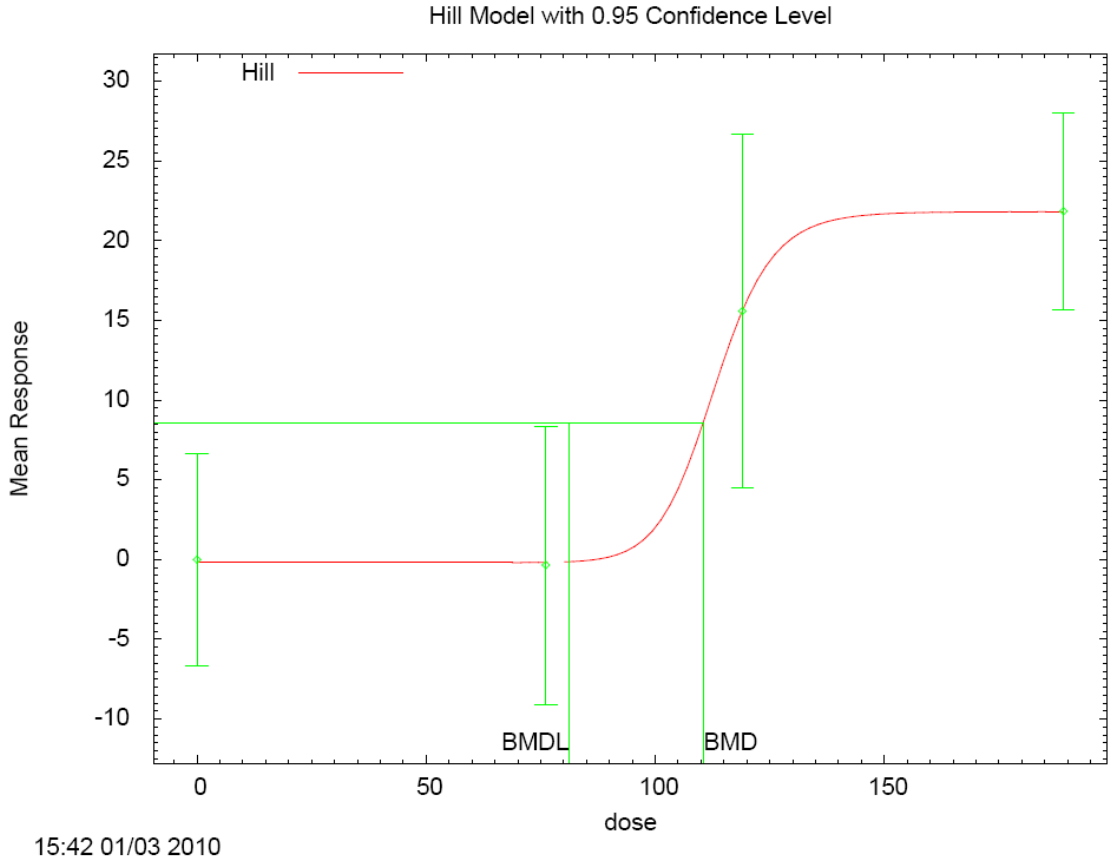
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-2. Predicted (Hill Model with Constant Variance) and Observed CAP Threshold Shifts at 12 kHz*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-3. Predicted (Hill Model with Constant Variance) and Observed CAP Threshold Shifts at 16 kHz*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

The $BMDL_{1SD}$ values estimated from the BMD model with the lowest AIC for CAP threshold data at 8, 12, and 16 kHz were 102.3, 89.47, and 81.10 µmol/L, respectively. The lowest $BMDL_{1SD}$ of 81.10 µmol/L was selected as the point of departure.

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: HECs were predicted from the $BMCL_{1SD}$ values (estimated from the model with the lowest AIC values) for CAP threshold data at 8, 12, and 16 kHz using the human PBPK model. The BMCL values for the internal dose metric (MCA) were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the BMCL. The HECs for $BMCL_{1SD}$ values are presented in Table A-3.

Table A-3. Human Equivalent Concentrations (HECs) for CAP Threshold Shifts

Effect	Model	$BMCL_{1SD}$ (µmol/L)	HEC[a] (ppm)
CAP threshold shift at 8 kHz	Polynomial (3-degree)	102.63	178.52
CAP threshold shift at 12 kHz	Hill	89.47	163.80
CAP threshold shift at 16 kHz	Hill	81.10	154.26

[a]Calculated using a reference human body weight of 70 kg and the assumption of 14-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric; CAP = compound action potential

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: There is limited information on the acute toxicity of ethylbenzene in humans. Acute exposures to ≥1,000 ppm resulted in ocular irritation, a burning sensation, and profuse lacrimation (Cometto-Muniz and Cain 1995; Thienes and Haley 1972; Yant et al. 1930). Volunteers exposed to 2,000 ppm reported irritation and chest constriction with worsening symptoms when the concentration was increased to 5,000 ppm (Yant et al. 1930). Studies in 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). Loss 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). 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). 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), suggesting that the auditory effects might be irreversible. 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).

Neurological 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).

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 exposure durations, 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 endoplasmic reticulum. An increase in relative kidney weight was also observed 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). No histopathological alterations were observed 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).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 42
Species: Rat

Minimal Risk Level: 2 [ ] 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 4th, 8th, and 13th week of exposure and at the end of the 8th 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 8th 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: $BMDL_{1SD}$ of 19.94 µmol/L for auditory shifts using an internal dose metric of time-averaged arterial blood concentration of ethylbenzene.

[] NOAEL [ ] LOAEL [x] BMCL

Auditory threshold shifts and OHC loss are selected as the critical effects following intermediate-duration inhalation exposure to ethylbenzene. Because these data are only presented graphically in the Gagnaire's paper, the data are not suitable for BMD analysis. However, Dr. Gagnaire has provided to ATSDR the individual animal data for these end points; these data are summarized in Tables A-4 and A-5.

Table A-4. Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Frequency (kHz)	Exposure duration (weeks)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB SPL)	SD	Number of rats
4						
	4					
		0	0	33	4	14
		200	20.97	31	4	13
		400	64.26	52	11	14
		600	118.07	75	7	14
		800	177.98	74	6	14
	13					
		0	0	31	4	14
		200	20.97	31	5	13
		400	64.26	59	8	14
		600	118.07	74	8	14
		800	177.98	73	7	14
8						
	4					
		0	0	22	4	14
		200	20.97	23	5	13
		400	64.26	40	11	14
		600	118.07	69	8	14
		800	177.98	68	6	14
	13					
		0	0	22	4	14
		200	20.97	21	4	13
		400	64.26	44	15	14
		600	118.07	71	9	14
		800	177.98	67	7	14

Table A-4. Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Frequency (kHz)	Exposure duration (weeks)	Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (dB SPL)	SD	Number of rats
16						
	4					
		0	0	21	3	14
		200	20.97	20	4	13
		400	64.26	40	16	14
		600	118.07	70	6	14
		800	177.98	68	5	14
	13					
		0	0	18	3	14
		200	20.97	18	4	13
		400	64.26	46	18	14
		600	118.07	74	9	14
		800	177.98	67	7	14

MCA = time-averaged arterial blood concentration of ethylbenzene; SD = standard deviation; SPL = sound pressure level

Source: Gagnaire et al. 2007

Table A-5. Percent OHC Loss in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks[a]

Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	Mean (% loss)	SD	Number of rats
0	0	0.346	0.159	7
200	20.97	3.67	4.24	8
400	64.26	67.12	12.26	8
600	118.07	85.58	7.68	8
800	177.98	90.81	7.36	8

[a]Evaluation conducted at the end of the 8-week recovery period.

MCA = time-averaged arterial blood concentration of ethylbenzene; OHC = outer hair cell; SD = standard deviation

Source: Gagnaire et al. 2007

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001) (see Appendix E for additional information on the PBPK model). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure

concentrations ranging from 1 to 50 ppm. For cochlear effects, the assumption was made that ethylbenzene, rather than a metabolite, is the toxic agent. Although there are no data for ethylbenzene, support of this assumption comes from studies of toluene (Pryor et al. 1991) and styrene (Ladefoged et al. 1998), which found that ototoxicity was most likely due to the action of the parent compound rather than a metabolite. The dose metric simulated for the cochlear effects was time-averaged arterial blood concentration of ethylbenzene (MCA) because there are no validated models for simulating ethylbenzene levels in cochlea tissue or endolymph. Using MCA for this endpoint assumes that tissue dosimetry and response would be correlated with time averaged arterial ethylbenzene concentrations (or average x time, AUC), which would be expected to correlate with time-averaged tissue concentration.

For the BMD analysis, the auditory threshold and percent OHC loss data were fit to all available continuous models in EPA's BMDS (version 2.1.1) using MCA as the dose metric. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For data sets that did not provide an adequate fit to the available models, the highest or two highest doses were dropped and the models were fit to the modified data set. ATSDR considered this an acceptable procedure because the BMD modeling was used to predict the response at low doses. For all models, a BMR of 1 standard deviation change from the control was used. This default BMR was used because there are insufficient mechanism of action data to determine what level of response constitutes a biologically significant effect in the cochlea.

The model predictions for auditory threshold after 4 and 13 weeks of exposures are presented in Tables A-6 and A-7. None of the BMD models provided an adequate fit (as assessed by the goodness-of-fit criteria) to the OHC loss data.

Table A-6. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
4 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.0004	<0.0001	382.99	NA	NA
Nonconstant variance					
Linear[b]	0.002	<0.0001	435.85	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	0.0002	0.0001	286.70	NA	NA
Nonconstant variance					
Linear[b]	0.007	<0.0001	312.35	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.001	216.31	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.66	<0.0001	207.43	NA	NA
Polynomial (2-degree)[c]	0.66	0.010	194.79	NA	NA
Power[c]	**0.66**	**0.21**	**189.65**	**58.75**	**33.12**
8 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.002	<0.0001	387.55	NA	NA
Nonconstant variance					
Linear[b]	0.004	<0.0001	438.09	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	0.001	0.002	291.87	NA	NA
Nonconstant variance					
Linear[b]	0.02	<0.0001	392.73	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	0.0003	0.05	211.83	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations				

Table A-6. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
were less than the number of parameters for the Hill model					
Linear[b]	0.61	0.01	200.49		
Polynomial (2-degree)[c]	**0.61**	**0.69**	**194.10**	**30.34**	**19.94**
Power[c]	0.61	NA	195.94	NA	NA
16 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	404.82	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	447.85	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.002	310.22	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	315.43	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.03	235.61	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.20	0.00	203.91	NA	NA
Polynomial (2-degree)[c]	0.20	0.07	195.17	NA	NA
Power[c]	**0.20**	**0.84**	**191.99**	**58.34**	**27.31**

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the BMC; NA = not applicable, model failed to provide an adequate fit to the data; SD = standard deviation

Source: Gagnaire et al. 2007

Table A-7. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
4 kHz frequency					
All doses					
Constant variance					
Linear[b]	0.05	<0.0001	385.41	NA	NA
Nonconstant variance					
Hill[c]	**0.64**	**0.93**	**322.34**	**54.91**	**28.59**
Linear[b]	0.64	<0.0001	437.05	NA	NA
Polynomial (2-degree)[c]	0.64	0.0001	419.18	NA	NA
Polynomial (3-degree)[c]	0.64	<0.0001	419.88	NA	NA
Polynomial (4-degree)[c]	0.64	<0.0001	414.64	NA	NA
Power[c]	0.64	<0.0001	375.90	NA	NA
8 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	408.00	NA	NA
Nonconstant variance					
Linear[b]	<0.0001	<0.0001	447.64	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.01	310.79	NA	NA
Nonconstant variance					
Linear[b]	0.001	<0.0001	402.37	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.01	233.73	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output, the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.78	<0.0001	213.91	NA	NA
Polynomial (2-degree)[c]	0.78	0.03	201.59	NA	NA
Power[c]	**0.78**	**0.54**	**197.02**	**58.29**	**29.71**
16 kHz frequency					
All doses					
Constant variance					
Linear[b]	<0.0001	<0.0001	434.87	NA	NA
Nonconstant variance					

Table A-7. Model Predictions for Changes in Auditory Thresholds in Male Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 13 Weeks

Model	Variance p-value[a]	Means p-value[a]	AIC	BMC_{1SD} (µmol/L)	$BMCL_{1SD}$ (µmol/L)
Linear[b]	<0.0001	<0.0001	474.46	NA	NA
Highest dose dropped					
Constant variance					
Linear[b]	<0.0001	0.03	322.19	NA	NA
Nonconstant variance					
Linear[b]	0.0001	<0.0001	416.55	NA	NA
2 Highest doses dropped					
Constant variance					
Linear[b]	<0.0001	0.01	245.83	NA	NA
Nonconstant variance					
Hill[c]	Failed to generate a model output, the number of observations were less than the number of parameters for the Hill model				
Linear[b]	0.34	<0.0001	211.61	NA	NA
Polynomial (2-degree)[c]	0.34	0.06	198.11	NA	NA
Power[c]	0.34	NA	196.52	NA	NA

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

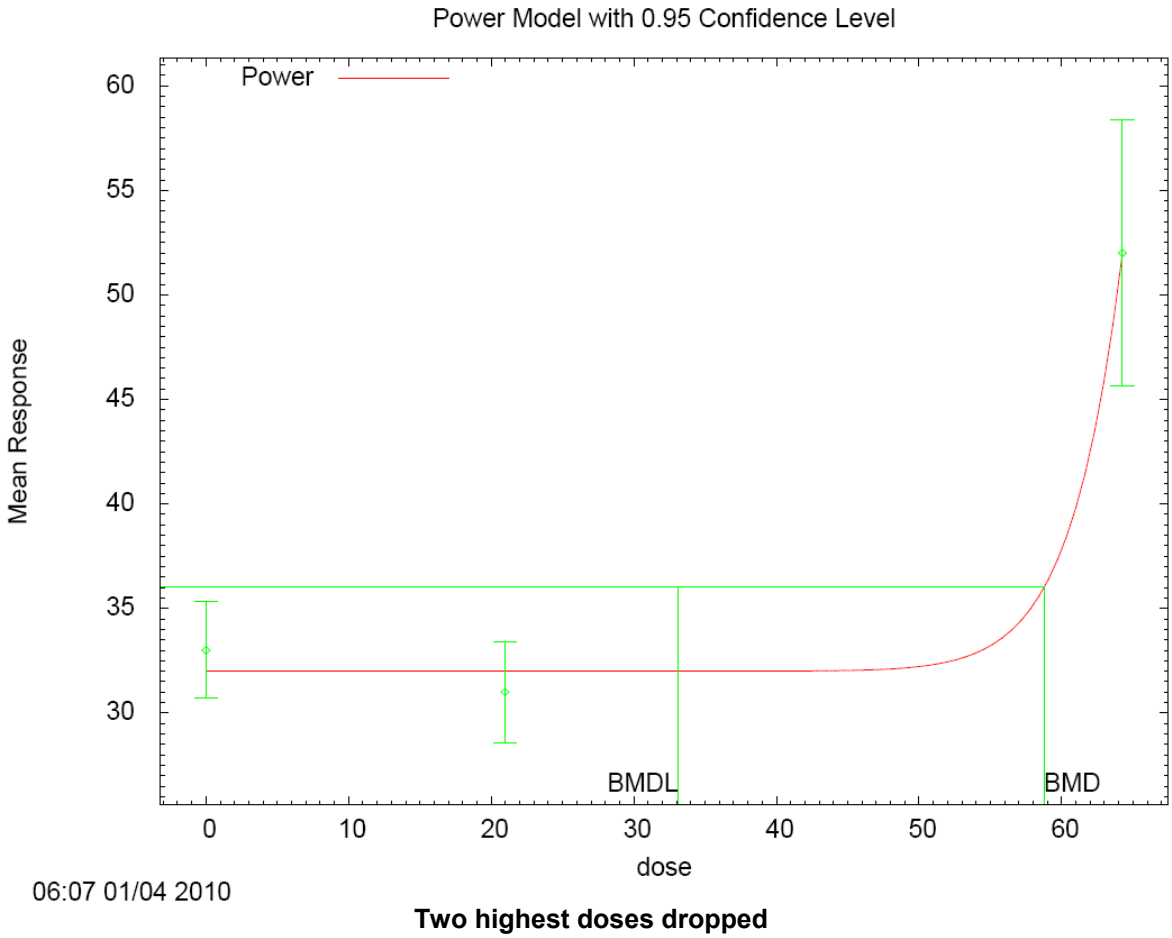
AIC = Akaike Information Criterion; BMC = benchmark concentration associated with a benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the BMC; NA = not applicable, model failed to provide an adequate fit to the data; SD = standard deviation

Source: Gagnaire et al. 2007

Most of the available BMDS models did not adequately fit the auditory threshold data; however, with the exception of the auditory thresholds at 16 kHz in rats exposed to ethylbenzene for 13 weeks, one BMD model fit each data set often when the highest two dose groups were dropped. In rats exposed to ethylbenzene for 4 weeks, the power with nonconstant variance, 2-degree polymonial with nonconstant variance, and power models adequately fit the auditory shift data assessed at 4, 8, or 16 kHz, respectively; these models are shown in Figures A-4, A-5, and A-6. The Hill model with nonconstant variance (Figure A-7) and the power model with nonconstant variance (FigureA- 8) adequately fit the auditory threshold shift data assessed at 4 and 8 kHz, respectively, for rats exposed for 13 weeks.

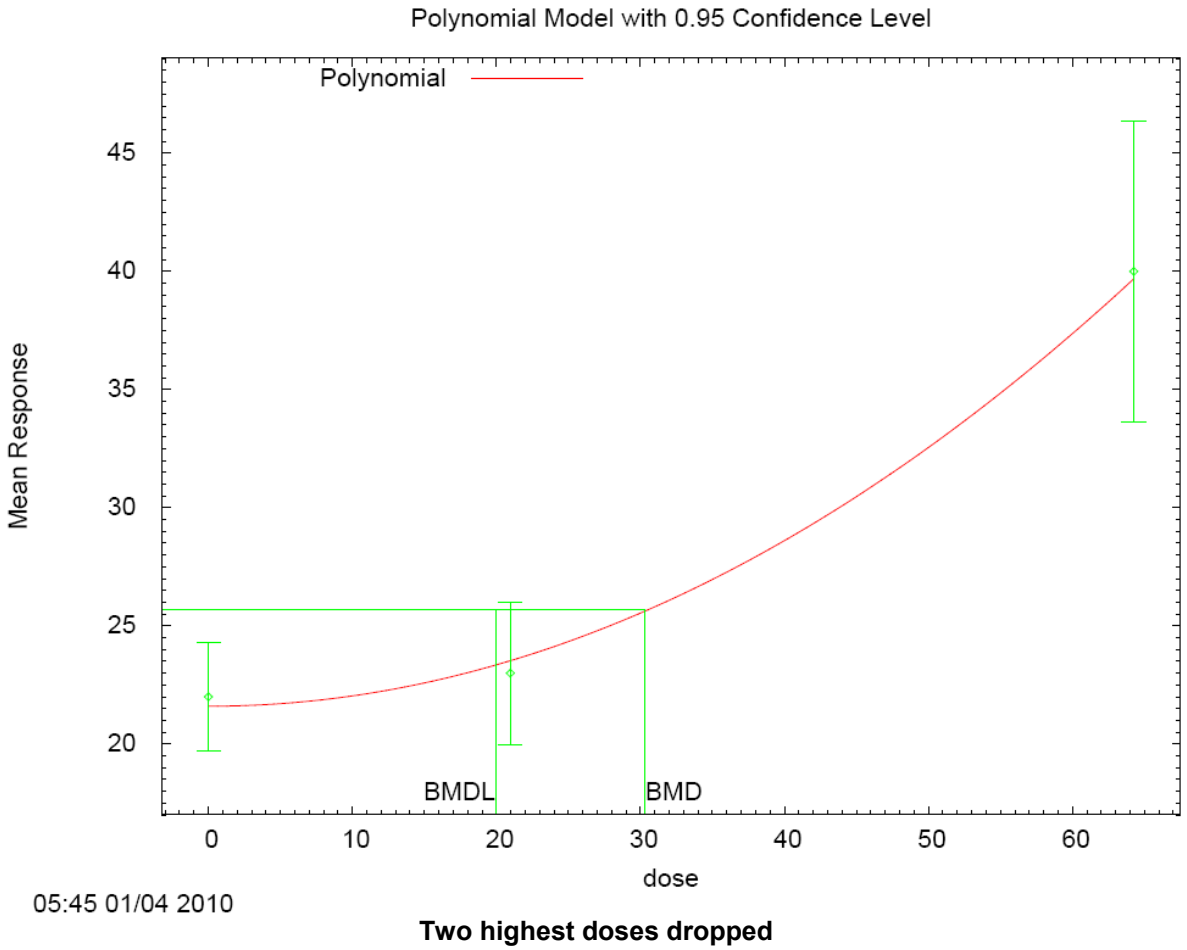
The $BMDL_{1SD}$ values estimated from the BMD model with the lowest AIC for changes in auditory threshold for each frequency and duration ranged from 19.94 to 33.21 µmol/L. Although there is a degree of uncertainty associated with the BMD models in which the two highest doses were dropped, the narrow range of BMCL values estimated from the truncated data sets and the full data set supports this approach. The lowest $BMDL_{1SD}$ of 19.94 µmol/L (estimated using auditory threshold data at 8 kHz following 4 weeks of exposure) was selected as the point of departure.

Figure A-4. Predicted (Power Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 4 kHz (4-Week Exposure)*



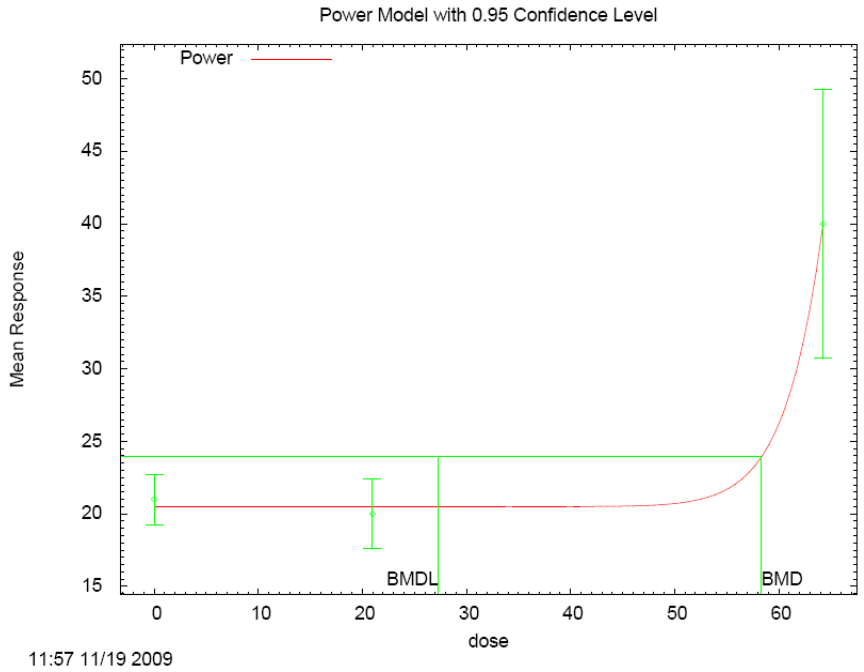
*BMCs and BMCLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-5. Predicted (2-Degree Polynomial Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 8 kHz (4-Week Exposure)*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

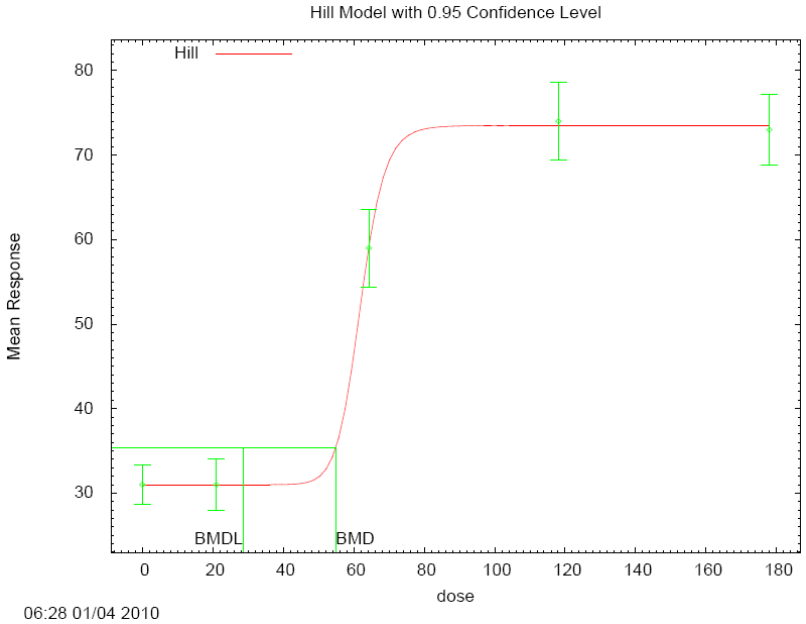
Figure A-6. Predicted (Power Model) and Observed Changes in Auditory Threshold at 16 kHz (4-Week Exposure)*



Two highest doses dropped

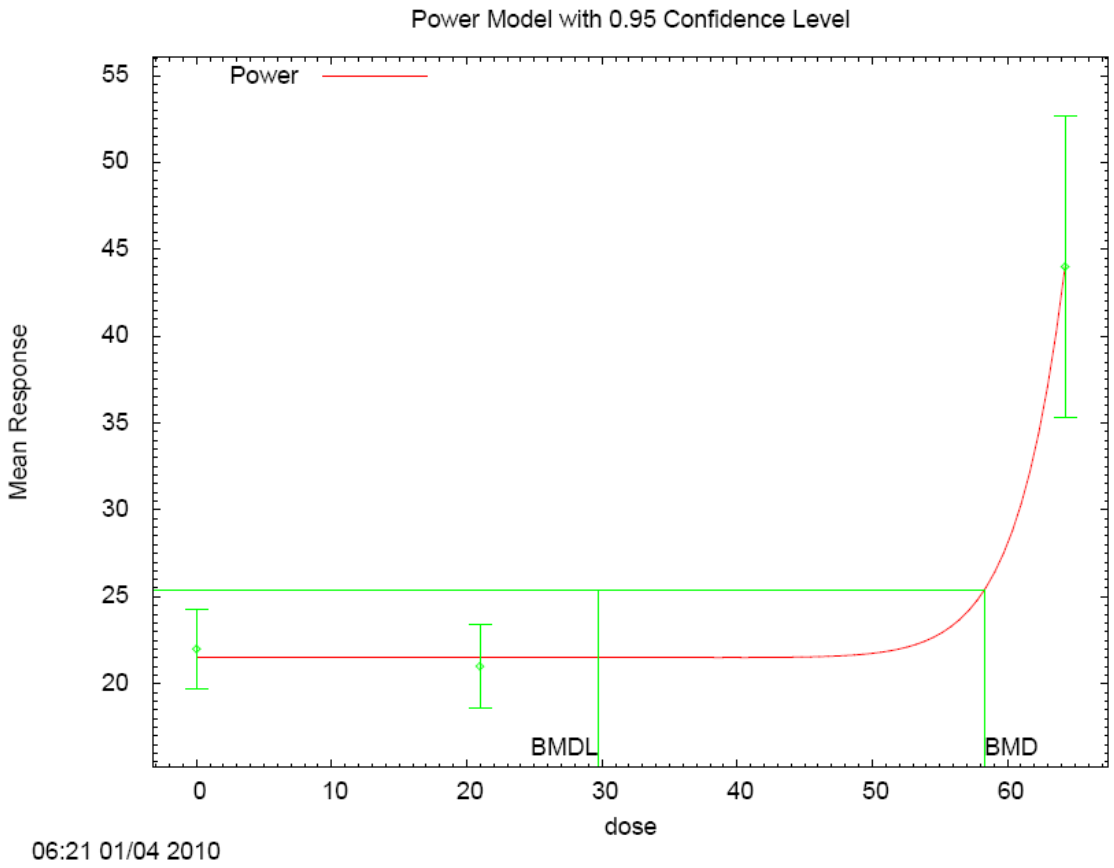
*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-7. Predicted (Hill Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 4 kHz (13-Week Exposure)*



*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control, and are in units of µmol/L.

Figure A-8. Predicted (Power Model with Nonconstant Variance) and Observed Changes in Auditory Threshold at 8 kHz (13-Week Exposure)*



Two highest doses dropped

*BMDs and BMDLs indicated are associated with a change of 1 standard deviation from the control and are in units of µmol/L.

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 concentration: The human PBPK model was used to predict HECs corresponding to specific BMCL values. The BMCL values for the internal dose metric (MCA) were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the BMCL. The HECs for $BMCL_{1SD}$ values estimated from the models providing adequate fit are listed in Table A-8. The HECs of the $BMCL_{1SD}$ values ranged from 63.64 to 87.13 ppm; the lowest HEC of 63.64 ppm was selected as the point of departure for the MRL.

Table A-8. Human Equivalent Concentrations for Auditory Effects in Sprague-Dawley Rats Exposed to Ethylbenzene 6 Hours/Day, 6 Days/Week for 4 or 13 Weeks

Effect	Model	$BMCL_{MCA}$ µmol/L)	HEC[a] (ppm)
Auditory thresholds at 4 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	33.12	87.13
Auditory thresholds at 8 kHz following 4 weeks of exposure	2-Degree polynomial (two highest doses dropped); nonconstant variance	19.94	63.64
Auditory thresholds at 16 kHz following 4 weeks of exposure	Power (two highest doses dropped); nonconstant variance	27.31	77.77
Auditory thresholds at 4 kHz following 13 weeks of exposure	Hill (all doses); nonconstant variance	28.59	79.95
Auditory thresholds at 8 kHz following 13 weeks of exposure	Power (two highest doses dropped); nonconstant variance	29.71	81.79

[a]Calculated using a reference human body weight of 70 kg and the assumption of 364-day continuous exposure.

$BMCL_{MCA}$ = 95% lower confidence limit on the benchmark concentration associated with a benchmark response of 1 standard deviation estimated using an MCA (time-weighted arterial blood concentration of ethylbenzene) dose metric

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: Several studies in animals, but no studies in humans, have examined the toxicity of ethylbenzene following intermediate-duration inhalation exposure. The available animal studies suggest that ototoxicity is the most sensitive end point of ethylbenzene toxicity. Rats exposed to ≥400 ppm ethylbenzene via inhalation for 4 or 13 weeks showed significant increases in auditory thresholds. 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.

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 250–1,000 ppm range (Cragg et al. 1989; Elovaara et al. 1985; NIOSH 1981; NTP 1992; Wolf et al. 1956). However, the changes in organ weight have not been associated with histological alterations. One study (Cragg et al. 1989) reported a small, but statistically significant, increase in platelet counts in male rats and leukocyte counts in female rats exposed to 782 ppm ethylbenzene for 4 weeks. Developmental effects have been observed in rats exposed to ≥1,000 ppm. Increases in the occurrence of skeletal malformations (NIOSH 1981; Saillenfait et al. 2003) and decreases in fetal body weight (Saillenfait et al. 2003, 2006, 2007) have been observed at ≥1,000 ppm. The NOAEL for these effects is 500 ppm (NIOSH 1981; Saillenfait et al. 2003, 2006, 2007). 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 study (Faber et al. 2006, 2007).

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Ethylbenzene
CAS Numbers: 100-41-4
Date: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 62
Species: Rat

Minimal Risk Level: 0.06 [ ] 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 (50 animals/sex/dose group) were exposed to 0, 75, 250, or 750 ppm ethylbenzene by inhalation for 6 hours/day, 5 days/week 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 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. Although the incidence of nephropathy (47/50, 43/50, 47/50, and 48/50 in males and 38/50, 42/50, 43/50, and 46/49 in females) was not significantly different between the groups, significant increases in the severity of the nephropathy were observed in females at ≥75 ppm and in males at 750 ppm. The nephropathy severity scores in the 0, 75, 250, and 750 ppm groups were 2.3, 2.4, 2.3, and 3.5 in males, respectively, and 1.3, 1.6, 1.7, and 2.3 in females, respectively. Additionally, significant increases in the incidences of renal tubule hyperplasia were observed in male rats exposed to 750 ppm. 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. An increase in the incidence of cystic degeneration of the liver was also observed in male rats at 750 ppm.

Dose and end point used for MRL derivation: The critical effect for chronic exposure to ethylbenzene is increased severity of chronic progressive nephropathy in female rats exposed to 75 ppm and higher (NTP 1999). BMD analysis was considered for determining the point of departure for the MRL; however, none of the available continuous exposure BMD models fit the data (standard errors were calculated using the raw severity score data). Thus, a NOAEL/LOAEL approach was selected for calculating the point of departure.

[ ] NOAEL [x] LOAEL

Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. Two internal dose metrics were simulated for kidney effects: time-averaged arterial blood concentration of ethylbenzene (MCA) and time-averaged rate of metabolism of ethylbenzene expressed per kg body mass (MRAMKB). Both metrics were explored because current knowledge of the mechanisms of toxicity of ethylbenzene does not include an understanding of the relative contribution of parent compound or metabolites as proximate toxic agents in kidney. The assumption in using the MCA metric for this end point is that tissue dosimetry and response would be correlated with time-averaged arterial ethylbenzene concentration (or average x time, AUC), which would be expected to correlate with time-averaged kidney concentration. The assumption in using the MRAMKB metric is that the kidney response is correlated with the time-averaged rate of whole-body production of ethylbenzene metabolites. In the model, all metabolism is attributed to the liver (the model does not have a kidney compartment); therefore, the rate of metabolism in the liver is the only representation of whole body metabolism that can be simulated. The internal dose metrics (MCA and MRAMKB) for each exposure level are presented in Table A-9.

Table A-9. Internal Dose Metrics for Male and Female F344/N Rats Exposed to Ethylbenzene 6 Hours/Day, 5 Days/Week for 104 Weeks

Exposure level (ppm)	Arterial ethylbenzene concentration (MCA, µmol/L)	MRAMKB (µmol/hour/kg body weight)
Male[a]		
0	0	0
75	4.12	8.92
250	27.66	23.64
750	146.77	43.05
Female[b]		
0	0	0
75	4.16	10.00
250	28.72	26.04
750	150.68	46.49

[a]Time weighted average body weight of 0.43 kg.
[b]Time weighted average body weight of 0.27 kg.

MCA = time-averaged arterial blood concentration; MRAMKB = time averaged rate of ethylbenzene metabolism expressed per kg body mass

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 PBPK model was used to predict HECs corresponding to $LOAEL_{MCA}$ and $LOAEL_{MRAMKB}$ in female rats. The MCA and MRAMKB dose metrics were converted to HEC values by iterative simulation of human inhalation exposures. Exposure concentrations were varied until the simulated value for the internal dose metric was within 0.01% of the LOAEL. The HECs were 17.45 ppm for the MCA dose metric and 52.68 ppm for the MRAMKB dose metric. Because there is limited information to determine whether the observed renal toxicity in female rats exposed to ethylbenzene is due to ethylbenzene or its metabolites, the lowest HEC value (17.45 ppm) was selected as the point of departure for the MRL.

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HECs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: The chronic toxicity of inhaled ethylbenzene has been examined humans and in 2-year bioassays in rats and mice conducted by NTP (1999). Hematological effects (increased average number of lymphocytes and decreased hemoglobin) were observed in workers exposed to solvents containing ethylbenzene (Angerer and Wulf 1985). In rats, concentration-related increases in the severity of nephropathy were observed in female rats exposed to ≥75 ppm and in male rats exposed to 750 ppm (NTP 1999). Increases in the incidence of renal tubule hyperplasia were also observed in male and female rats exposed to 750 ppm. The lowest LOAEL identified in mice was 250 ppm for hyperplasia of pituitary gland pars distalis observed in females; at 750 ppm, thyroid follicular cell hyperplasia was observed in male and female mice and hypertrophy and necrosis of the liver were observed in male mice.

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: June 2010
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.4 [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 (alanine aminotransferase and γ-glutamyl transferase) 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) (Table A-10). 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.

Table A-10. Effects on Serum Liver Enzymes, Liver Weights, and Liver Histopathology in Male and Female Rats Exposed to Oral Ethylbenzene for 13 Weeks

Parameter	Dose group (mg/kg/day)			
	0	75	250	750
		Males		
ALT (µkat/L)	0.62±0.12[a]	0.70±0.12	0.89±0.26[b]	1.11±0.23[b]
GGT (nkat/L)	2±3	6±6	10±6[b]	10±6[b]
Absolute liver weight (g)	8.02±0.55	8.26±0.81	10.25±0.98[b]	9.88±0.98[b]
Liver/body weight (%)	2.26±0.08	2.36±0.08[b]	3.01±0.14[b]	3.31±0.13[b]
Centrilobular hepatocyte hypertrophy (incidence)	1/10	1/10	6/10[c]	8/10[b]
		Females		
ALT(µkat/L)	0.58±0.18	0.55±0.08	0.60±0.12	0.73±0.19[c]
Absolute liver weight (g)	5.40±0.30	5.72±0.53	6.11±0.36[b]	7.15±0.50[b]
Liver/body weight (%)	2.63±0.13	2.70±0.16	3.03±0.12[b]	3.52±0.18[b]
Centrilobular hepatocyte hypertrophy (incidence)	0/10	0/10	5/10[c]	10/10[b]

[a]values are mean±standard deviation.
[b]p≤0.01.
[c]p≤0.05.

ALT = alanine aminotransferase; GGT = γ-glutamyl transferase

Source: Mellert et al. 2007

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 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 250 and 750 mg/kg/day groups in males, but only in the 750 mg/kg/day group in females, males appeared more sensitive than females to hepatic effects of oral ethylbenzene. BMD analysis was used to identify points of departure for several liver endpoints (alanine aminotransferase activity,

γ-glutamyl transferase activity, absolute liver weight, relative liver weight, and centrolobular hepatocyte hypertrophy) using the two internal dose metrics.

[ ] NOAEL [ ] LOAEL [X] BMDL

To determine the point of departure for derivation of the intermediate-duration MRL, a PBPK model was used to estimate internal dose metrics and data sets for serum liver enzymes, absolute and relative liver weight, and centrilobular hepatocyte hypertrophy (Table A-10) in male rats were evaluated for suitability for BMD modeling. Code for an ethylbenzene inhalation PBPK model was developed from documentation provided in Tardif et al. (1997) with revised metabolism parameter values reported in Haddad et al. (1999, 2001). This model reproduces model output reported in Tardif et al. (1997) for venous blood and alveolar air concentrations of ethylbenzene in rats and humans and output reported in Appendix R of American Chemistry Council (2007, Krishnan simulations) of human steady-state venous blood and alveolar air concentrations for exposure concentrations ranging from 1 to 50 ppm. The model was extended to implement first-order gastrointestinal absorption kinetics as described in Faber et al. (2006). For liver effects, the model simulated two internal dose metrics: time-averaged concentration of ethylbenzene in liver (MCL) and time-averaged rate of metabolism of ethylbenzene in liver (MRAMKL). The assumption of using the MCL metric is that the liver response is correlated with the time-averaged concentration of ethylbenzene in liver. The assumption in using the MRAMKL metric is that the liver response is correlated with the time-averaged rate of production of ethylbenzene metabolites in liver. Both metrics were explored because current knowledge of the mechanism of toxicity of ethylbenzene does not include an understanding of the relative contributions of parent compound or metabolites as proximate toxic agents in liver.

Data for changes in alanine aminotransferase and γ-glutamyl transferase, absolute liver weight and relative liver weight were analyzed using all available continuous variable models in EPA BMDS (version 2.1.1). BMDs and the 95% lower confidence limit on the BMD (BMDLs) associated with a BMR of 1 standard deviation change from the control were calculated for all models. The data were fit to BMD models using the MCL and MRAMKL internal dose metrics. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power and Hill models are fit to the data and evaluated while the variance model is applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling.

As summarized in Table A-11, the alanine aminotransferase activity data only adequately fit the Hill model (Figure A-9) and absolute liver weight data only fit the linear model with nonconstant variance (Figure A-10) when MCL was used as the internal dose metric. Three models fit the data (using MCL as the internal dose metric) for relative liver weight when the highest dose was dropped (linear, 2-degree polynomial, and power models); the linear model is presented in Figure A-11. No models meet adequate fit criteria for γ-glutamyl transferase when MCL was used as the internal dose metric.

Table A-11. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, and Absolute and Relative Liver Weight Using Liver Ethylbenzene Concentration (MCL) Dose Metric in Male Rats Exposed to Ethylbenzene Via Gavage for 13 Weeks Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/L)	$BMDL_{1SD}$ (μmol/L)
Alanine aminotransferase					
All doses					
Constant variance					
Linear[b]	0.02	0.04	-83.16	NA	NA
Nonconstant variance					
Hill[c]	**0.34**	**0.83**	**-93.15**	**21.34**	**7.49**
Linear[b]	0.34	0.001	-82.16	NA	NA
Polynomial (2-degree)[b]	0.34	0.001	-82.16	NA	NA
Polynomial (3-degree)[b]	0.34	0.001	-82.16	NA	NA
Power[c]	0.34	0.001	-82.16	NA	NA
γ-Glutamyl transferase	Inadequate fit to all models				
Absolute liver weight					
All doses					
Constant variance					
Hill[c]	0.28	NA	33.68	NA	NA
Linear[b]	0.28	<0.0001	56.22	NA	NA
Polynomial (2-degree)[b]	0.28	<0.0001	56.22	NA	NA
Polynomial (3-degree)[b]	0.28	<0.0001	56.22	NA	NA
Power[c]	0.28	<0.0001	56.22	NA	NA
Highest dose dropped					
Constant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	**0.20**	**0.87**	**19.46**	**42.31**	**32.17**
Polynomial (2-degree)[b]	0.20	0.87	19.46	42.31	32.17
Power[c]	0.20	0.87	19.46	42.31	32.17
Relative liver weight					
All doses					
Constant variance					

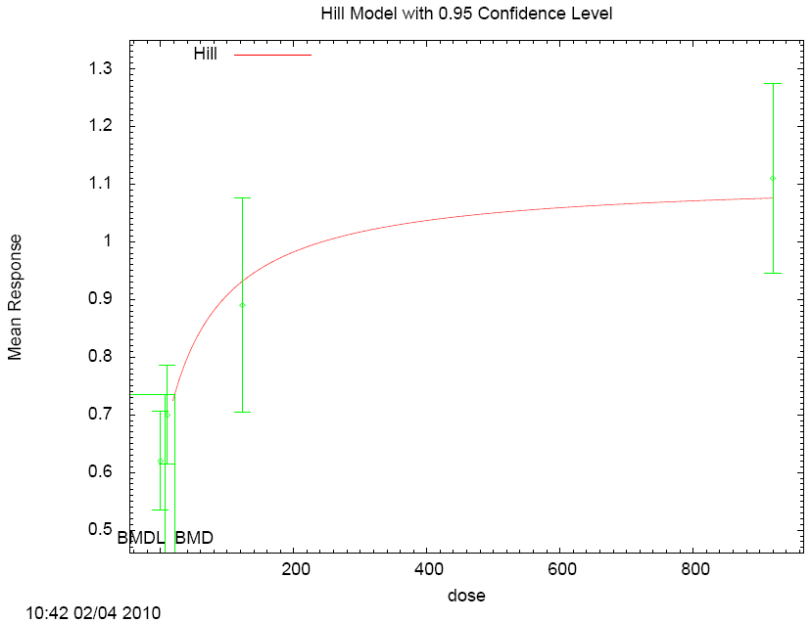
Table A-11. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, and Absolute and Relative Liver Weight Using Liver Ethylbenzene Concentration (MCL) Dose Metric in Male Rats Exposed to Ethylbenzene Via Gavage for 13 Weeks Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/L)	$BMDL_{1SD}$ (μmol/L)
Hill[c]	0.15	NA	-130.06	NA	NA
Linear[b]	0.15	<0.0001	-60.07	NA	NA
Polynomial (2-degree)[b]	0.15	<0.0001	-60.07	NA	NA
Polynomial (3-degree)[b]	0.15	<0.0001	-60.07	NA	NA
Power[c]	0.15	<0.0001	-60.07	NA	NA
Highest dose dropped					
Constant variance					
Hill[c]	Failed to generate a model output; the number of observations were less than the number of parameters for the Hill model				
Linear[b]	**0.11**	**0.39**	**-102.26**	**16.74**	**13.53**
Polynomial (2-degree)[b]	0.11	0.39	-102.26	16.74	13.53
Power[c]	0.11	0.39	-102.26	16.74	13.53

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

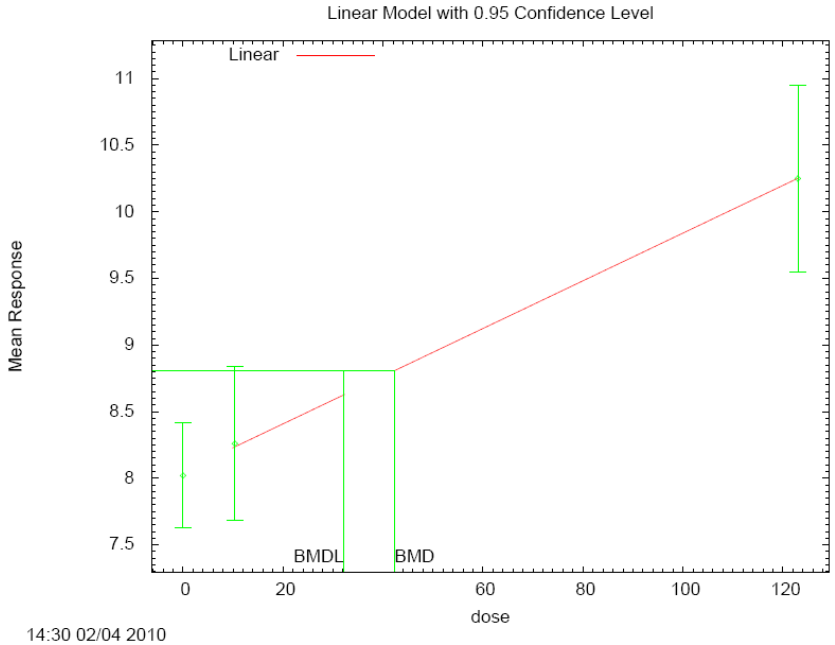
AIC = Akaike Information Criterion; BMD_{1SD} = benchmark dose associated with the benchmark response of 1 standard deviation (SD); BMDL = 95% lower confidence limit on the BMD; MCL = time-averaged concentration of ethylbenzene in liver; NA = not applicable, model does not provide adequate fit to the data

Figure A-9. Predicted (Hill Model with Nonconstant Variance) and Observed Changes in Alanine Aminotransferase Levels Using MCL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

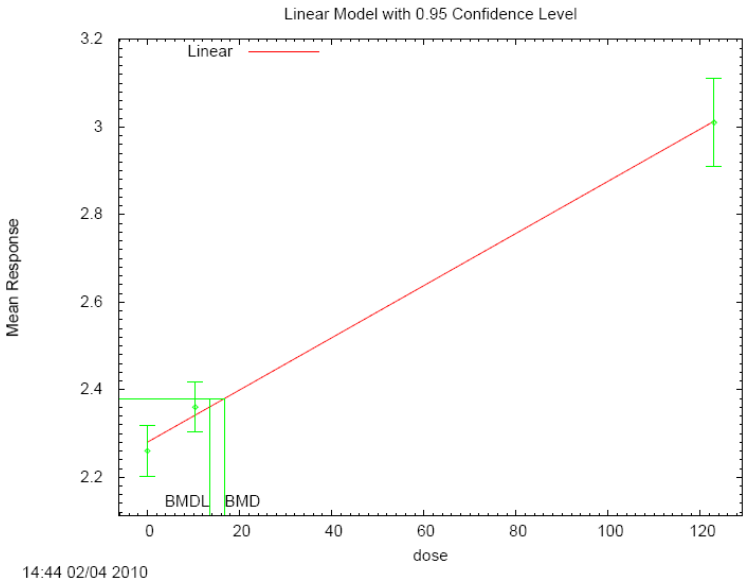
Figure A-10. Predicted (Linear Model with Constant Variance) and Observed Changes in Absolute Liver Weight Using MCL Internal Dose Metric*



Highest dose dropped

*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

Figure A-11. Predicted (Linear Model with Constant Variance) and Observed Changes in Relative Liver Weight Using MCL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of umol/L.

The model predictions using the MRAMKL internal dose metric are summarized in Table A-12. Several models fit the alanine aminotransferase data, the 3-degree polynomial model with nonconstant variance had the lowest AIC and is illustrated in Figure A-12. The linear, 2-degree polynomial, 3-degree polynomial, and power models all meet adequate fit criteria to the γ-glutamyl transferase data; Figure A-13 shows the fit of the linear model. The Hill model (Figure A-14) was the only model which provided adequate fit to the absolute liver weight data. Several models fit the relative liver weight data, the 2-degree polynomial model provided the best fit, as judged by the AIC; this model is shown in Figure A-15.

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Alanine aminotransferase					
All doses					
Constant variance					
Linear[b]	0.02	0.14	-85.87	NA	NA
Nonconstant variance					

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Hill[c]	0.34	NA	-90.93	NA	NA
Linear[b]	0.34	0.26	-92.47	438.99	307.25
Polynomial (2-degree)[b]	0.34	0.65	-92.98	771.05	387.82
Polynomial (3-degree)[b]	**0.34**	**0.81**	**-93.14**	**804.09**	**391.02**
Power[c]	0.34	0.61	-92.93	778.16	388.97
γ-Glutamyl transferase					
All doses					
Constant variance					
Hill[c]	0.14	NA	180.82	NA	NA
Linear[b]	**0.14**	**0.73**	**177.46**	**1,072.23**	**737.62**
Polynomial (2-degree)[b]	0.14	0.73	177.46	1,072.23	737.62
Polynomial (3-degree)[b]	0.14	0.73	177.46	1,072.23	737.62
Power[c]	0.14	0.73	177.46	1,072.23	737.62
Absolute liver weight					
All doses					
Constant variance					
Hill[c]	**0.28**	**0.31**	**31.68**	**602.99**	**548.01**
Linear[b]	0.28	0.05	34.73	NA	NA
Polynomial (2-degree)[b]	0.28	0.01	36.61	NA	NA
Polynomial (3-degree)[b]	0.28	0.01	36.61	NA	NA
Power[c]	0.28	0.02	36.29	NA	NA
Relative liver weight					
All doses					
Constant variance					
Hill[c]	0.15	NA	-130.06	NA	NA
Linear[b]	0.15	<0.0001	-107.43	NA	NA
Polynomial (2-degree)[b]	**0.15**	**0.96**	**-133.98**	**531.76**	**390.47**

Table A-12. Model Predictions for Changes in Alanine Aminotransferase, γ-Glutamyl Transferase, Absolute Liver Weight, and Relative Liver Weight in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

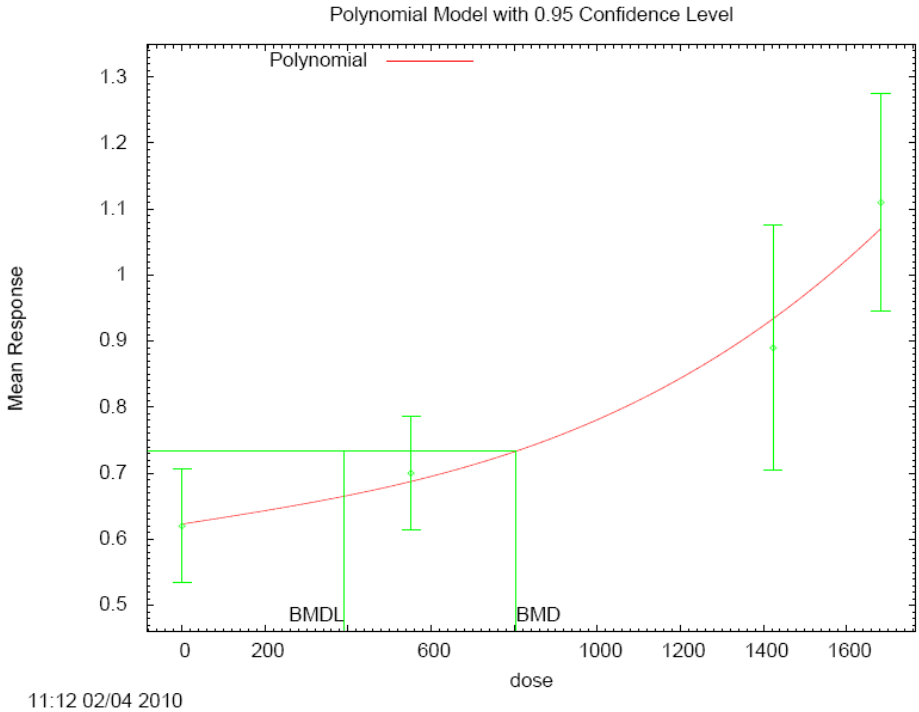
Model	Variance p-value[a]	Means p-value[a]	AIC	BMD_{1SD} (μmol/hour/kg liver)	$BMDL_{1SD}$ (μmol/hour/kg liver)
Polynomial (3-degree)[b]	0.15	0.80	-132.00	540.34	485.79
Power[c]	0.15	0.83	-132.02	547.45	416.38

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Coefficients restricted to be positive.
[c]Power restricted to ≥1.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response of 1 standard deviation (SD); BMDL = 95% lower confidence limit on the BMD; MRAMKL = time-averaged rate of metabolism of ethylbenzene in liver; NA = not applicable, model does not provide adequate fit to the data.

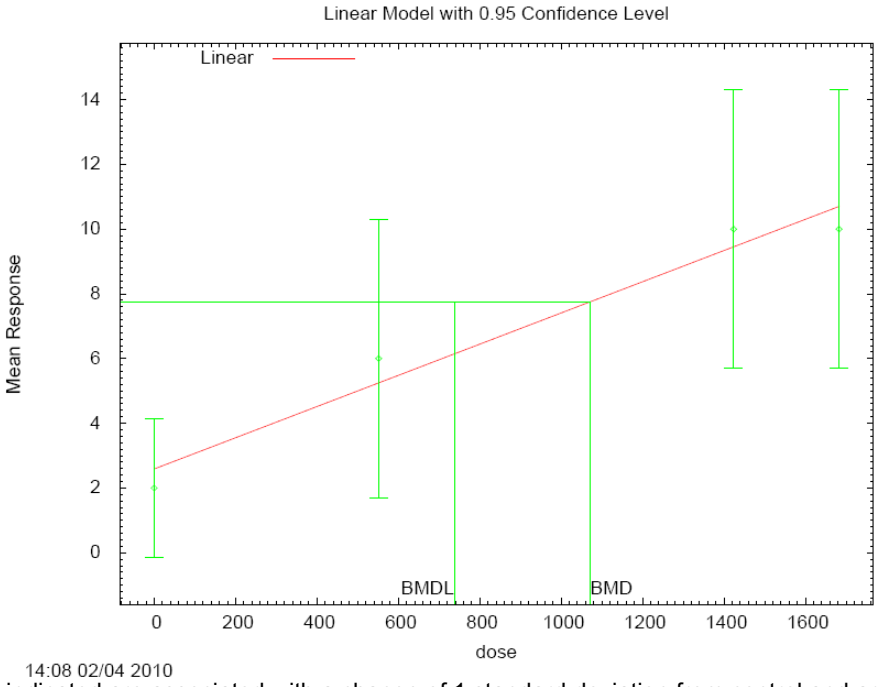
Source: Mellert et al. 2007

Figure A-12. Predicted (3-Degree Polynomial with Nonconstant Variance) and Observed Changes in Alanine Aminotransferase Using MRAMKL Internal Dose Metric*



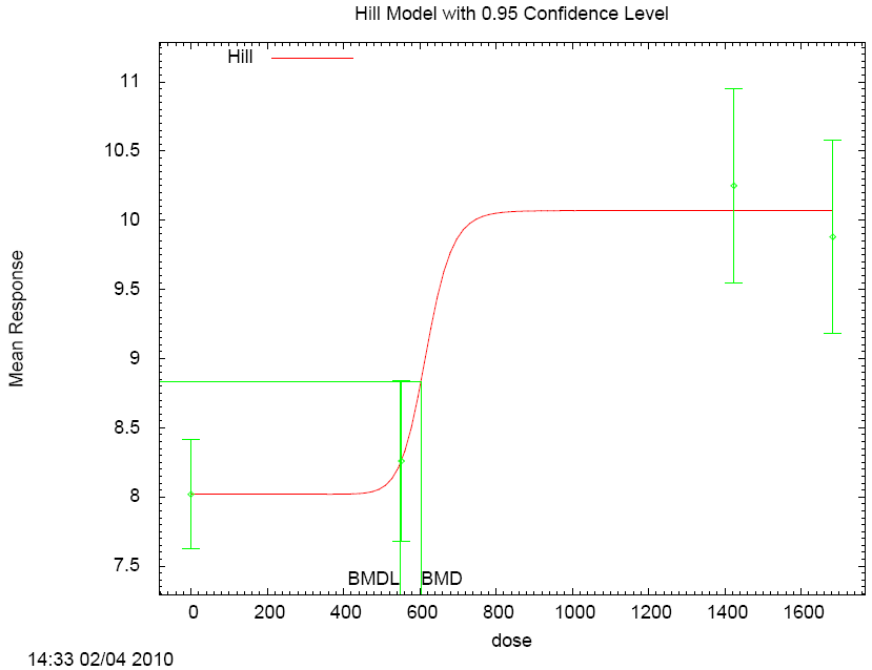
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-13. Predicted (Linear Model with Nonconstant Variance) and Observed Changes in γ-Glutamyl Transferase Using MRAMKL Internal Dose Metric*



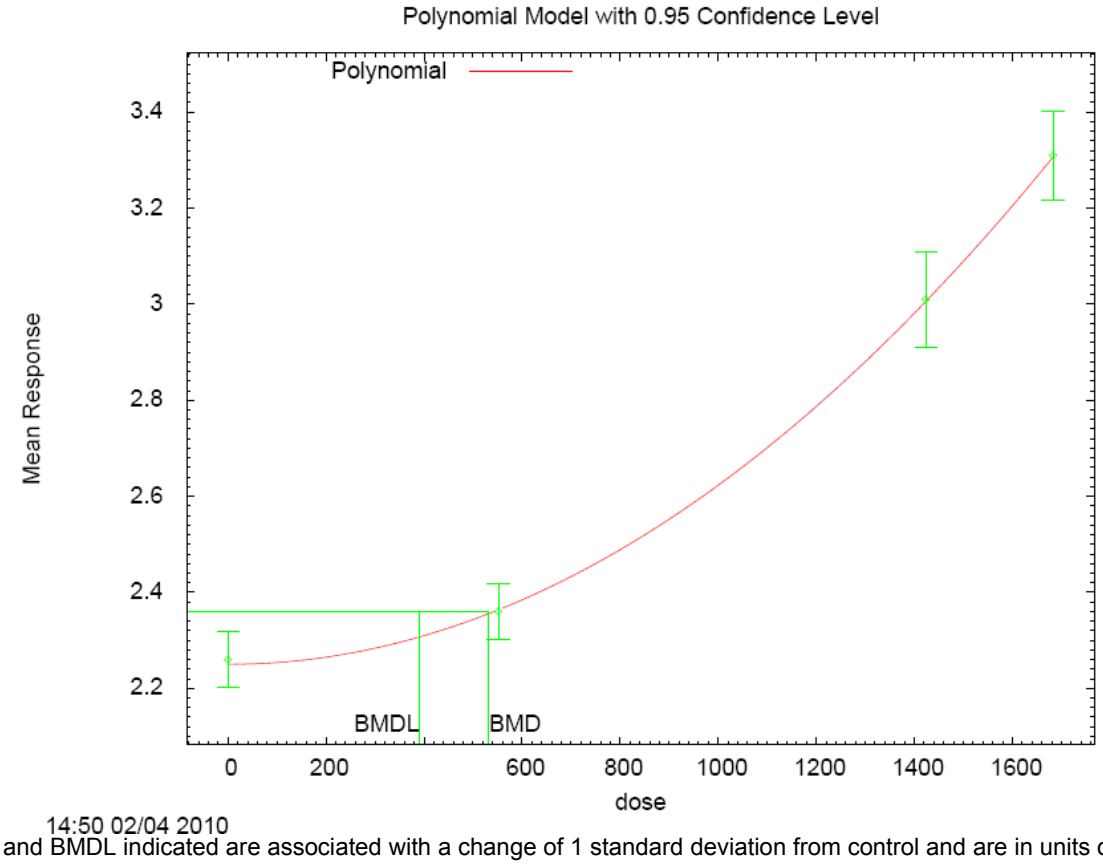
*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-14. Predicted (Hill Model with Constant Variance) and Observed Changes in Absolute Liver Weight Using MRAMKL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of μmol/hour/kg liver.

Figure A-15. Predicted (2-Degree Polynomial Model with Constant Variance) and Observed Changes in Relative Liver Weight Using MRAMKL Internal Dose Metric*



*BMD and BMDL indicated are associated with a change of 1 standard deviation from control and are in units of µmol/hour/kg liver.

Data for the incidence of centrilobular hepatocyte hypertrophy were analyzed using all available dichotomous models in the EPA BMDS (version 2.1.1) using the extra risk option. The multistage model was run for all polynomial degrees up to n-1 (where n is the number of dose groups including control). Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all the models meeting adequate fit criteria, the lowest BMDL was selected as the point of departure when the difference between the BMDLs estimated from these models were more than 3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. BMDs and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk were calculated for all models. The data were fit to BMD models using the MCL and MRAMKL dose metrics. The BMD models using the MCL dose metric are summarized in Table A-13. As assessed by the chi-square goodness-of-fit statistic, most of the models using the MCL dose metric provided adequate fit to the data. The BMDs ranged from 16.51 to 127.56 µmol/L and the BMDLs ranged from 6.61 to 76.55 µmol/L. Because the range of BMDLs was greater than threefold; the lowest BMDL was selected as a point of departure. The log logistic model estimated the lowest BMDL of 6.61 µmol/L; the fit of this model is presented in Figure A-16.

Table A-13. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to Ethylbenzene via Gavage for 13 Weeks Using MCL Internal Dose Metric

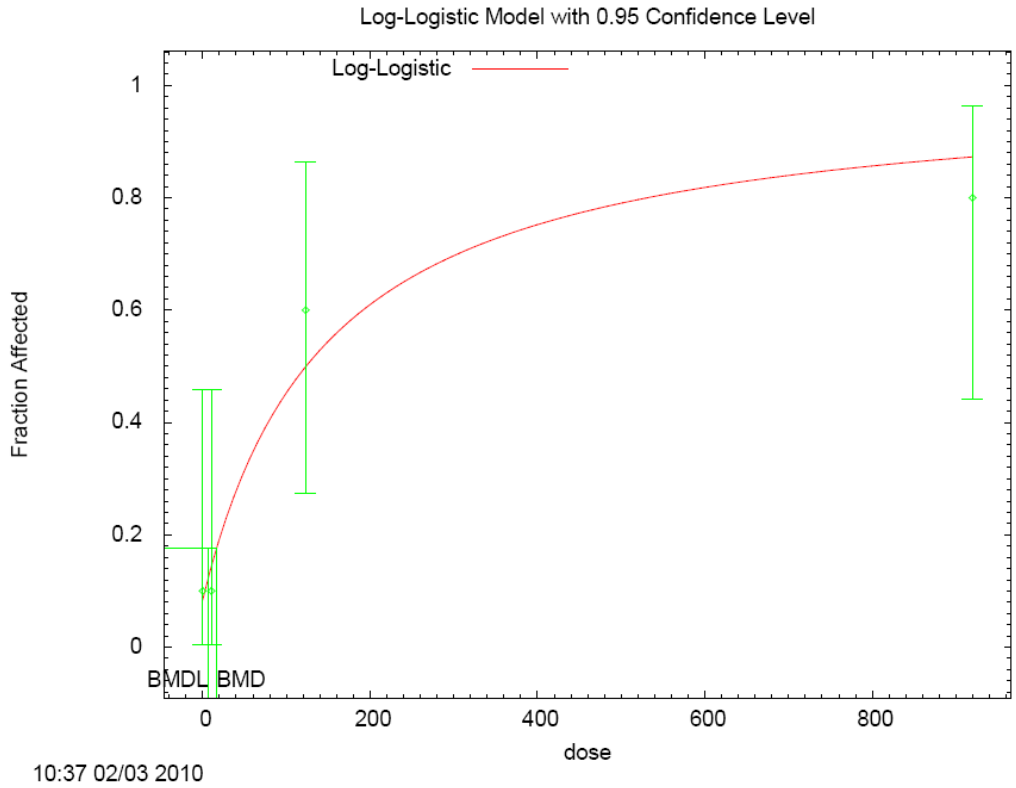
Model	χ^2 Goodness-of-fit p-value[a]	AIC	BMD_{10} (µmol/L)	$BMDL_{10}$ (µmol/L)
Gamma[b]	0.13	44.25	48.12	26.42
Logistic	0.04	46.66	127.56	76.55
Log Logistic	**0.59**	**41.50**	**16.51**	**6.61**
Log Probit	0.07	44.67	NA	NA
Multistage (1-degree polynomial)[c]	0.13	44.25	48.12	26.42
Multistage (2-degree polynomial)[c]	0.13	44.25	48.12	26.42
Multistage (3-degree polynomial)[c]	0.13	44.25	48.12	26.42
Probit	0.04	46.62	NA	NA
Weibull[b]	0.13	44.25	48.12	26.42
Quantal-Linear	0.13	44.25	48.12	26.42

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Betas restricted to ≥0.

AIC = Akaike Information Criteria; BMD = benchmark dose associated with the selected benchmark response of 10% extra risk; BMDL = 95% lower confidence limit on the BMD; NA = not applicable, the data did not adequately fit the model

Source: Mellert et al. 2007

Figure A-16. Predicted (Log Logistic Model) and Observed Incidence of Centrilobular Hepatocyte Hypertrophy*



*BMDs and BMDLs indicated are associated with 10% extra risk and are in units of µmol/L.

The BMD models using the MRAMKL dose metric are presented in Table A-14. All models provided adequate fit to the data (χ^2 p>0.1). Comparing across models, a better fit is generally indicated by a lower AIC. As assessed by AIC, the multistage 3-degree polynomial model (Figure 17) provided the best fit to the data. The BMD_{10} and $BMDL_{10}$ predicted by this model for the data on centrilobular hepatocyte hypertrophy in male rats were 704.21 and 206.91 µmo/hour/kg liver, respectively.

Because there is limited information to determine whether the observed hepatic effects are due to ethylbenzene or its metabolites, the lowest BMDL value (6.61 µmol/L, MCL dose metric) was selected as the point of departure for the MRL.

Table A-14. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Administered Ethylbenzene Via Gavage for 13 Weeks Using MRAMKL Internal Dose Metric

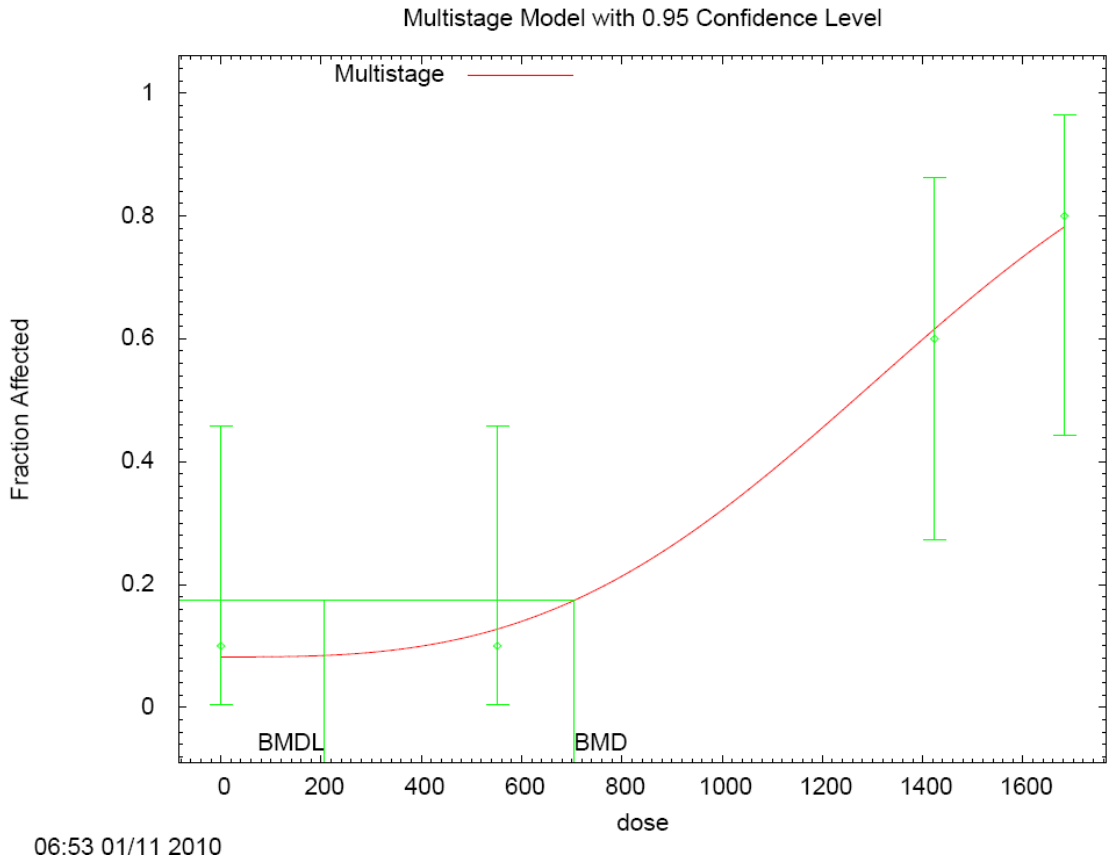
Model	χ^2 Goodness-of-fit p-value[a]	AIC	BMD_{10} (µmol/hour/kg liver)	$BMDL_{10}$ (µmol/hour/kg liver)
Gamma[b]	0.99	42.47	937.22	283.42
Logistic	0.62	41.38	480.93	300.24
Log Logistic	0.98	42.47	961.63	313.44
LogProbit	1.00	42.47	973.00	332.90
Multistage (1-degree polynomial)[c]	0.18	44.50	178.95	113.79
Multistage (2-degree polynomial)[c]	0.65	41.42	483.71	179.74
Multistage (3-degree polynomial)[c]	**0.93**	**40.61**	**704.21**	**206.91**
Probit	0.55	41.64	426.74	278.66
Weibull[b]	0.88	42.49	849.57	267.67
Quantal-Linear	0.18	44.50	178.95	113.79

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria
[b]Power restricted to ≥1
[c]Betas restricted to ≥0

AIC = Akaike Information Criteria; BMD = benchmark dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: Mellert et al. 2007

Figure A-17. Predicted (Multistage, 3-Degree Polynomial Model) and Observed Incidence of Centrilobular Hepatocyte Hypertrophy*



*BMDs and BMDLs indicated are associated with 10% extra risk and are in units of µmol/hour/kg liver.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a less serious LOAEL
[x] 3 for extrapolation from animals to humans with dosimetric adjustments
[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: For each end point and dose metric, human equivalent doses (HEDs) were predicted for the BMDL value with the lowest AIC (if multiple BMD models met the adequate fit criteria) using the human PBPK model. The BMDL values for the internal dose metrics (MCL and MRAMKL) were converted to HED values by iterative simulation of human oral exposures. Exposure doses (mg/kg/day) were varied until the simulated value for the internal dose metric was within 0.01% of the BMDL. The HEDs are summarized in Tables A-15 and A-16.

Table A-15. Human Equivalent Doses for Liver Effects Using MCL Internal Dose Metric

Effect	Model	BMDL (µmol/L)	HED[a] (mg/kg/day)
Increased alanine aminotransferase	Hill (all doses); constant variance	7.49	11.82
Increased γ-glutamyl transferase	Inadequate fit to all models		
Increased absolute liver weights	Linear (highest dose dropped); constant variance	32.17	31.82
Increased relative liver weights	Linear (highest dose dropped); constant variance	13.53	18.47
Centrilobular hepatocyte hypertrophy	Log logistic	6.61	10.68

[a]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).

BMDL = 95% lower confidence limit on the benchmark dose; HED = human equivalent dose; MCL = time-averaged concentration of ethylbenzene in liver

Table A-16. Human Equivalent Doses for Liver Effects Using MRAMKL Internal Dose Metric

Effect	Model[a]	BMDL (µmol/hour/kg liver)	HED[b] (mg/kg/day)
Increased alanine aminotransferase	3-Degree polynomial; nonconstant variance	391.02	31.06
Increased γ-glutamyl transferase	Linear; constant variance	737.62	111.37[c]
Increased absolute liver weights	Hill; constant variance	548.01	48.62
Increased relative liver weights	2-Degree polynomial; constant variance	390.47	31.01
Centrilobular hepatocyte hypertrophy	Multistage (3-degree polynomial)	206.91	15.48

[a]All doses used for BMD modeling.
[b]Calculated using a reference human body weight of 70 kg and the assumption that the daily dose was delivered in 16 dose splits/24 hours (i.e., only exposed during waking hours).
[c]Approximate value, value is very close to the metabolism Vmax.

BMDL = 95% lower confidence limit on the benchmark dose; MRAMKL = time-averaged rate of metabolism of ethylbenzene in liver

Was a conversion used from intermittent to continuous exposure? The PBPK models used to estimate internal dose metrics and HEDs adjusted for intermittent exposure.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration oral database for ethylbenzene is limited to a study conducted 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). The 4- and 13-week studies by Mellert et al. (2007) found effects consistent with hepatotoxicity including increased absolute and relative liver weights, increased incidence of hepatocyte centrilobular hypertrophy, and increased serum liver enzyme activities in rats administered ≥250 mg/kg/day. Kidney effects, including increases in increases in relative kidney weight and hyaline droplet nephropathy were observed in males administered ≥250 mg/kg/day; however, these effects were most likely secondary to increases accumulation of accumulation of α2μ-globulin accumulation, and, therefore, considered not relevant to humans. Wolf et al. (1956) also reported liver effects (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. 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.

Acute (Cappaert et al. 1999, 2000, 2001, 2002) and intermediate (Gagnaire et al. 2007) inhalation studies and an acute oral study (Gagnaire and Langlais 2005) have identified ototoxicity as a sensitive effect of ethylbenzene exposure. Although intermediate-duration oral studies have not examined this potential endpoint, a comparison of the human equivalent dose for liver effects following oral exposure and the human equivalent concentration for ototoxicity following inhalation exposure can be made using the PBPK model developed for MRL derivation. The human PBPK model predicts that the HED (10.68 mg/kg/day) would result in an internal dose of 1.92 μmol/L for MCA (the relevant internal dose metric for ototoxicicty). The HEC that corresponds to an MCA of 1.92 μmol/L is 8.37 ppm. Therefore, the HED of 10.68 mg/kg/day would be equivalent to human equivalent air concentration of 8.37 ppm. This air concentration is about 8-fold lower than the HEC of 63.64 ppm used to derive the intermediate-duration inhalation MRL, suggesting that the liver is a more sensitive target of oral toxicity than the cochlea.

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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

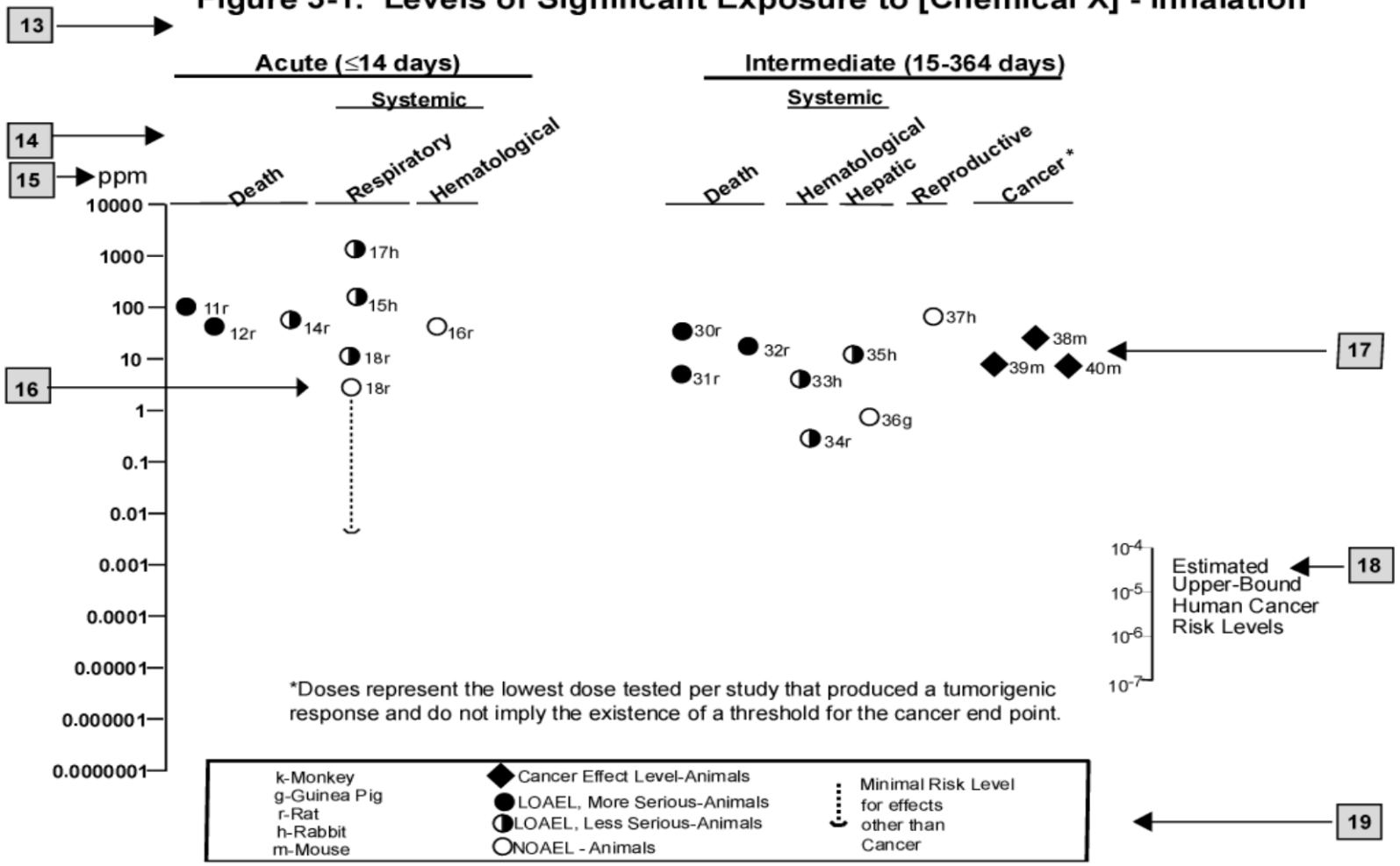
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → 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/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
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

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