APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Benzene
CAS Numbers: 71-43-2
Date: August 2007
Profile Status: Post Public, Final Draft
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 46
Species: Mouse

Minimal Risk Level: 0.009 [ ] mg/kg/day [x] ppm

Reference: Rozen MG, Snyder CA, Albert RE. 1984. Depression in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol Lett 20:343-349.

Experimental design: Male C57BL/6J mice (7–8/group) were exposed to benzene (0, 10.2, 31, 100, or 301 ppm) in whole-body dynamic inhalation chambers for 6 hours/day for 6 consecutive days. Control mice were exposed to filtered, conditioned air only. Erythrocyte counts were depressed in C57BL/6 mice only at 100 and 301 ppm. The 10.2 ppm exposure level resulted in significant depression of femoral lipopolysaccharide-induced B-colony-forming ability in the absence of a significant depression of total numbers of B cells. At 31 ppm, splenic phytohemagglutinin-induced blastogenesis was significantly depressed without a concomitant significant depression in numbers of T-lymphocytes. Peripheral lymphocyte counts were depressed at all exposure levels. These results demonstrate that short-term inhaled benzene even at low exposure concentrations can alter certain immune associated processes.

Effect noted in study and corresponding doses:

10.2 ppm = No adverse effect on erythrocytes, depressed peripheral lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes (less serious LOAEL).

31 ppm = No adverse effect on erythrocytes, depression of mitogen-induced blastogenesis of splenic T-cells.

100 ppm = Depressed erythrocyte counts.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

Uncertainty Factors used in MRL derivation: 300

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans using dosimetric conversion)
[ ] 1 [ ] 3 [x] 10 (for human variability)

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10.2 ppm) by 6/24 to correct for less than a full day of exposure. The resulting $LOAEL_{ADJ}$ is 2.55 ppm.

According to current EPA (1994b) methodology for calculating a human equivalent concentration (HEC) for extrarespiratory effects of a category 3 gas (such as benzene):

$$LOAEL_{HEC} = LOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$$

where:

$LOAEL_{HEC}$ = The LOAEL dosimetrically adjusted to a human equivalent concentration

$LOAEL_{ADJ}$ = The LOAEL adjusted from intermittent to continuous exposure

$[H_{b/g}]_A/[H_{b/g}]_H$ = The ratio of the blood:gas partition coefficient of the chemical for the laboratory animal species to the human value

If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the ratio. According to Wiester et al. (2002), benzene blood:gas partition coefficients for mice and humans are 17.44 and 8.12, respectively. Therefore the default value of 1 is applied, in which case, the $LOAEL_{HEC}$ is equivalent to the $LOAEL_{ADJ}$ = 2.55 ppm.

Was a conversion used from intermittent to continuous exposure? The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10.2 ppm) by 6/24 to correct for less than a full day of exposure. The resulting $LOAEL_{ADJ}$ is 2.55 ppm.

Other additional studies or pertinent information that lend support to this MRL: Increased number of micronucleated polychromatic erythrocytes (MN-PCEs), decreased numbers of granulopoietic stem cells (Toft et al. 1982), lymphopenia (Cronkite et al. 1985), lymphocyte depression, and increased susceptibility to bacterial infection (Rosenthal and Snyder 1985) are among the adverse hematological and immunological effects observed in several other acute-duration inhalation studies. The study by Rozen et al. (1984) shows benzene immunotoxicity (reduced mitogen-induced lymphocyte proliferation) at a slightly lower exposure level than these other studies. C57BI/6J mice were exposed to 0, 10.2, 31, 100, and 301 ppm benzene for 6 days at 6 hours/day. Lymphocyte counts were depressed at all exposure levels while erythrocyte counts were elevated at 10.2 ppm, equal to controls at 31 ppm, and depressed at 100 and 301 ppm. Femoral B-lymphocyte and splenic B-lymphocyte numbers were reduced at 100 ppm. Levels of circulating lymphocytes and mitogen-induced blastogenesis of femoral B-lymphocytes were depressed after exposure to 10.2 ppm benzene for 6 days. Mitogen-induced blastogeneses of splenic T-lymphocytes were depressed after exposure to 31 ppm of benzene for 6 days. In another study, mice exhibited a 50% decrease in the population of erythroid progenitor cells (CFU-E) after exposure to 10 ppm benzene for 5 days, 6 hours/day (Dempster and Snyder 1991). In a study by Wells and Nerland (1991), groups of 4–5 male Swiss-Webster mice were exposed to 0, 3, 25, 55, 105, 199, 303, 527, 1,150, or 2,290 ppm benzene for 6 hours/day for 5 days. The number of leukocytes in peripheral blood and spleen weights were significantly decreased compared with untreated controls at all concentrations ≥25 ppm. Therefore, 3 ppm was the NOAEL and 25 ppm was the LOAEL for these effects. Other end points were not monitored in this study. These data support the choice of Rozen et al. (1984) as a critical study.

Agency Contacts (Chemical Managers): Sharon Wilbur, M.A., Sam Keith, M.S., C.H.P., Obaid Faroon, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Benzene
CAS Numbers: 71-43-2
Date: August 2007
Profile Status: Post Public, Final Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 126
Species: Mouse

Minimal Risk Level: 0.006 [ ] mg/kg/day [x] ppm

Reference: Rosenthal GJ, Snyder CA. 1987. Inhaled benzene reduces aspects of cell-mediated tumor surveillance in mice. Toxicol Appl Pharmacol 88:35-43.

Experimental design: Male C57Bl/6 mice were exposed to 10, 30, or 100 ppm of benzene by inhalation 6 hours/day, 5 days/week for 20 exposure days. The number of lymphocytes and their functional capacities were evaluated in spleens of exposed mice. Following the 20 days of exposure, functional capacity of splenic lymphocytes was evaluated in two *in vitro* assays: mixed-lymphocyte culture (MLC) and 51Cr-release cytotoxicity assay. Measured mean daily benzene concentrations in the 10, 30, and 100 ppm groups were 11.1 (±1.5) ppm, 29.5 (±4.4) ppm, and 99.7 (±7.0) ppm, respectively. No changes were observed in the relative proportions of splenic leukocytes, in the percentage of T-cell subsets or in the ratio of T-helper and T-suppressor cells, even at the highest exposure level (100 ppm). Therefore, the functional assays could be normalized for particular lymphocyte populations by using equal numbers of splenic cells. MLC is an *in vitro* measure of alloreactivity (capacity to mount an immune response against foreign antigens). The MLC activity of spleen lymphocytes from 10- and 100-ppm mice was delayed on days 2–4 of culture (relative to air-exposed controls), indicating that benzene exposure causes impaired in vitro alloreactivity (data for the 30-ppm mice were not included in the reported results). This delayed alloreactivity was not due to spleen suppressor cells. The lymphocyte cytotoxic function evaluated in the 51Cr-release assay was also altered; splenic lymphocytes from 100-ppm mice had a significantly reduced lysing capacity. The results indicate that inhalation exposure of mice to benzene has an immunodepressive effect on *in vitro* alloreactivity and cytotoxicity of splenic lymphocytes.

Effect noted in study and corresponding doses:

10 ppm = Significantly delayed splenic lymphocyte reaction to foreign antigens evaluated in *in vitro* mixed lymphocyte reaction (less serious LOAEL).

30 ppm = Results not reported.

100 ppm = Significantly delayed splenic lymphocyte reaction to foreign antigens evaluated in *in vitro* mixed lymphocyte reaction.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

Uncertainty Factors used in MRL derivation: 300

[ ] 1 [ ] 3 [x] 10 (for use of a LOAEL)
[ ] 1 [x] 3 [ ] 10 (for extrapolation from animals to humans using dosimetric conversion)
[ ] 1 [ ] 3 [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: According to current EPA (1994b) methodology for calculating a human equivalent concentration (HEC) for extrarespiratory effects of a category 3 gas (such as benzene):

$LOAEL_{HEC} = LOAEL_{ADJ} \times ([H_{b/g}]_A/[H_{b/g}]_H)$

where:

$LOAEL_{HEC}$ = The LOAEL dosimetrically adjusted to a human equivalent concentration

$LOAEL_{ADJ}$ = The LOAEL adjusted from intermittent to continuous exposure

$[H_{b/g}]_A/[H_{b/g}]_H$ = The ratio of the blood:gas partition coefficient of the chemical for the laboratory animal species to the human value

If the animal blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the ratio. According to Wiester et al. (2002), benzene blood:gas partition coefficients for mice and humans are 17.44 and 8.12, respectively. Therefore, the default value of 1 is applied, in which case, the $LOAEL_{HEC}$ is equivalent to the $LOAEL_{ADJ}$.

Was a conversion used from intermittent to continuous exposure? The concentration was adjusted for intermittent exposure by multiplying the LOAEL (10 ppm) by 6 hours/24 hours to correct for less than a full day of exposure and 5 days/7 days to correct for less than a full week of exposure. The resulting $LOAEL_{ADJ}$ is 1.8 ppm.

Other additional studies or pertinent information that lend support to this MRL: Exposure of C57BL mice to 10 ppm benzene for 6 hours/day, 5 days/week caused significant depressions in numbers of lymphocytes (ca. 30% lower than controls) as early as exposure day 32; this effect was also noted at the other scheduled periods of testing (exposure days 66 and 178) (Baarson et al. 1984). Splenic red blood cells were significantly reduced (ca. 15% lower than controls) at exposure days 66 and 178. The failure of the erythrons of benzene-exposed mice to support normal red cell mass was illustrated by the significant reduction in peripheral red cell numbers in these animals at 66 and 178 days of benzene exposure. Green et al. (1981a, 1981b) exposed male CD-1 mice to benzene vapors at concentrations of 0 or 9.6 ppm for 6 hours/day, 5 days/week for 50 days and assessed the effects of exposure on cellularity in the spleen, bone marrow, and peripheral blood. Exposure-related effects included a 90% increase in numbers of multipotential hematopoietic stem cells (CFU-S) (Green et al. 1981a), approximately 25% increase in spleen weight and total splenic nucleated cellularity (Green et al. 1981b), and 80% increase in nucleated RBCs (Green et al. 1981b). The results of Baarson et al. (1984) and Green et al. (1981a, 1981b) are limited for purposes of quantitative risk assessment because a single exposure level was employed. However, they support the choice of Rosenthal and Snyder (1987) as the critical study, which serves as the basis for the intermediate-duration inhalation MRL.

Agency Contacts (Chemical Managers): Sharon Wilbur, M.A., Sam Keith, M.S., C.H.P., Obaid Faroon, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Benzene
CAS Numbers: 71-43-2
Date: August 2007
Profile Status: Post Public, Final Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 161
Species: Human

Minimal Risk Level: 0.003 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Lan Q, Zhang L, Li G, et al. 2004a. Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774-1776.

Experimental design: A cross-sectional study was performed on 250 workers (approximately two-thirds female) exposed to benzene at two shoe manufacturing facilities in Tianjin, China, and 140 age- and gender-matched workers in clothing manufacturing facilities that did not use benzene. The benzene-exposed workers had been employed for an average of 6.1±2.9 years. Benzene exposure was monitored by individual organic vapor monitors (full shift) 5 or more times during 16 months prior to phlebotomy. Post-shift urine samples were collected from every worker. Urinary benzene concentrations were highly correlated with mean individual air levels. Benzene was not found (detection limit 0.04 ppm) in workplace and home air samples of control workers taken at three different time periods. Study subjects were categorized into four groups (140 controls, 109 at <1 ppm, 110 at 1–<10 ppm, and 31 at ≥10 ppm) according to mean benzene exposure levels measured twice during the month prior to phlebotomy. Of the 250 exposed workers, 109 were exposed to <1 ppm benzene. Each of these individuals worked at the larger of the two facilities included in the study. Exposure concentrations were generally higher at the smaller facility due to a less adequate ventilation system. Complete blood count (CBC) and differential were analyzed mechanically. Coefficients of variation for all cell counts were <10%.

Mean 1-month benzene exposure levels in the four groups (controls, <1 ppm, 1–<10 ppm, and ≥10 ppm) were <0.04, 0.57±0.24, 2.85±2.11, and 28.73±20.74 ppm, respectively (see Table A-1). An evaluation of potential confounding factors showed that age, gender, cigarette smoking, alcohol consumption, recent infection, and body mass index were associated with at least one hematological end point. The values in Table A-1 represent values that were adjusted to account for these variables. All types of white blood cells (WBCs) and platelets were significantly decreased in the lowest exposure group (<1 ppm), ranging in magnitude from approximately 8 to 15% lower than controls. Although similar statistical analyses for the mid- and high-exposure groups were not included in the study report, decreases in all types of WBCs and platelets were noted at these exposure levels as well; the decreases in the highest exposure group ranged in magnitude from 15 to 36%. Lymphocyte subset analysis revealed significantly decreased CD4+-T cells, CD4+/CD8+ ratio, and B cells. Hemoglobin concentrations were significantly decreased only within the highest (≥10 ppm) exposure group. Tests for a linear trend using benzene air level as a continuous variable were significant for platelets and all WBC measures except monocytes and CD8+-T cells. Upon restricting the linear trend analyses to workers exposed to <10 ppm benzene, excluding controls, inverse associations remained for total WBCs, granulocytes, lymphocytes, B cells, and platelets. In order to evaluate the effect of past benzene exposures on the hematological effects observed in this study, the authors compared findings for a group of workers who had been exposed to <1 ppm benzene over the previous year (n=60) and a subset who also had <40 ppm-years lifetime cumulative benzene exposure (n=50). The authors stated that the same cell types were significantly reduced in these groups, but did not provide further information of the magnitude (i.e., percent change) of

the hematological effects observed. These data suggest that the 1-month benzene exposure results could be used as an indicator of longer term low-level benzene hematotoxicity. To demonstrate that the observed effects were attributable to benzene, significantly decreased levels of WBCs, granulocytes, lymphocytes, and B cells were noted in a subgroup (n=30; mean 1-month exposure level of 0.29±0.15 ppm) of the <1 ppm group for which exposure to other solvents was negligible.

Table A-1. Significantly Reduced Blood Values in Workers Exposed to Benzene in Tianjin, China (Adapted from Lan et al. 2004a)

	Mean exposure level in ppm[a] (number of subjects)			
End point	<0.04 (140)	0.57±0.24 (109)	2.85±2.11 (110)	28.73±20.74 (31)
WBCs[b]	6,480±1,710	5,540±1,220[d]	5,660±1,500	4,770±892
Granulocytes[b]	4,110±1,410	3,360±948[d]	3,480±1,170	2,790±750
Monocytes[b]	241±92	217±97[d]	224±93	179±74
Lymphocytes[b]	2,130±577	1,960±541[d]	1,960±533	1,800±392
CD4+-T cells[b]	742±262	635±187[d]	623±177	576±188
CD4+/CD8+ ratio	1.46±0.58	1.26±0.41[d]	1.22±0.45	1.09±0.35
B cells[b]	218±94	186±95[d]	170±75	140±101
Platelets[c]	230±59.7	214±48.8[d]	200±53.4	172±44.8

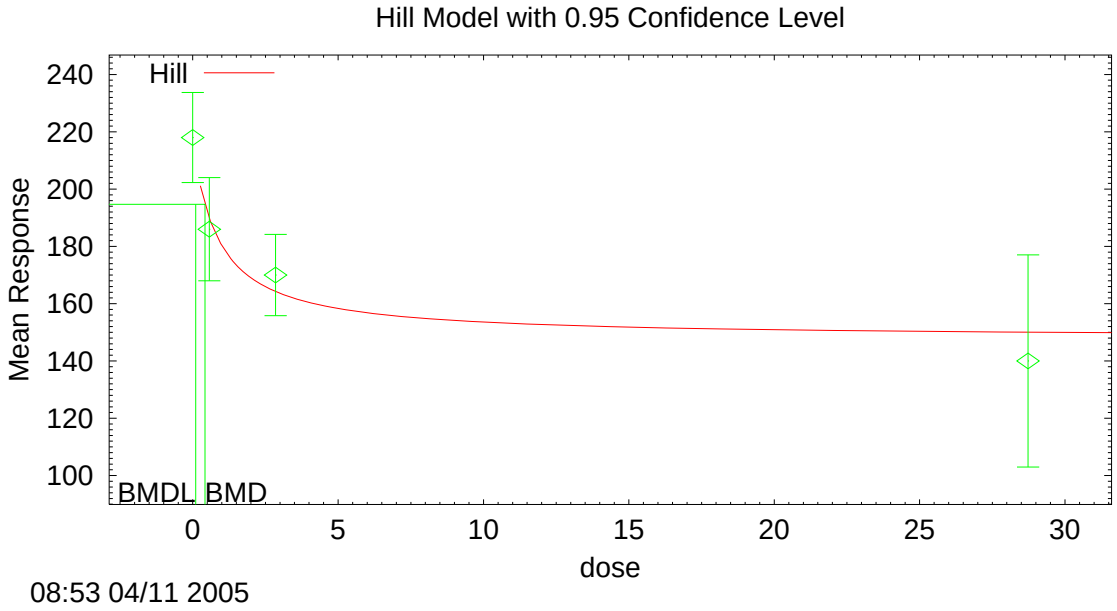
[a]Arithmetic mean of an average of two measurements per subject collected during the month prior to phlebotomy
[b]Mean cell numbers per microliter blood±standard deviation
[c]Mean number of platelets ($x10^3$)
[d]Statistically significantly lower than controls ($p<0.05$) by linear regression on ln of each end point

Effect noted in study and corresponding doses: As shown in Table A-1, exposure-response relationships were noted for several blood factors. Benzene-induced decreased B cell count was selected as the critical effect for benchmark dose (BMD) modeling because it represented the highest magnitude of effect (i.e., B cell count in the highest exposure group was approximately 36% lower than that of controls). A BMD modeling approach was selected to identify the point of departure because the critical study (Lan et al. 2004a) identified a LOAEL in the absence of a NOAEL.

Dose and end point used for MRL derivation: 0.10 ppm ($BMCL_{0.25sd}$) for decreased B cell count.

All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the B cell count data shown in Table A-1. Visual inspection of the plots of observed versus expected values for B cell counts indicated that the Hill model provided the only adequate fit of the data set (see Figure A-1). A benchmark response (BMR) of 0.25 sd below the control mean B cell count was selected because it resulted in a $BMC_{0.25sd}$ of 0.42 ppm and its lower 95% confidence limit ($BMCL_{0.25sd}$) of 0.10 ppm (Figure A-1), which are below the mean exposure level of the lowest exposure group (0.57 ppm) for which a statistically significant decrease in mean B cell count (186 versus 218 in controls, see Table A-1) was observed. Although Lan et al. (2004a, 2004b) noted significantly decreased levels of WBCs, granulocytes, lymphocytes, and B cells in a subgroup (n=30; mean 1-month exposure level of 0.29±0.15 ppm) of the 0.57 ppm exposure group, this subgroup could not be included in the BMD analysis because the study authors did not include the means and standard deviations for the decreased blood factors, nor did they provide quantitative information regarding the remaining 70 subjects in the 0.57 ppm exposure group (n=109). Assuming that the 0.29 ppm exposure level may represent a minimally adverse exposure level, it seems reasonable to accept the $BMCL_{0.25sd}$ of 0.10 ppm as the point of departure for deriving a chronic-duration inhalation MRL for benzene.

Figure A-1. Observed and Predicted B Cell Counts in Human Subjects Occupationally Exposed to Benzene. BMD=$BMC_{0.25sd}$=0.42 ppm; BMDL=$BMCL_{0.25sd}$=0.10 ppm



The computer output for fitting of the Hill model to B cell counts in human subjects occupationally exposed to benzene (Lan et al. 2004a) follows.

```
==============================================================================
        Hill Model. $Revision: 2.1 $ $Date: 2000/10/11 21:21:23 $
        Input Data File: C:\ATSDR\BENZENE\BMD FILES\BENZENELANBCELLS.(d)
        Gnuplot Plotting File:  C:\ATSDR\BENZENE\BMD
FILES\BENZENELANBCELLS.plt
                                          Mon Nov 20 09:27:13 2006
 ==============================================================================

 BMDS MODEL RUN
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)

   Dependent variable = MEAN
   Independent variable = ppm
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

Default Initial Parameter Values

alpha =	8224.64	
rho =	0	Specified
intercept =	218	
v =	-78	
n =	0.572459	
k =	1.5675	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -n have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	alpha	rho	intercept	v	k
alpha	1	0	0	0	0
rho	0	1	0	0	0
intercept	0	0	1	0	0
v	0	0	0	1	0
k	0	0	0	0	1

Parameter Estimates

Variable	Estimate	Std. Err.
alpha	8027.09	1
rho	0	1
intercept	217.113	1
v	-69.0144	1
n	1	NA
k	0.878186	1

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	140	218	94	217	89.6	0.0099
0.57	109	186	95	190	89.6	-0.0441
2.85	110	170	75	164	89.6	0.063
28.73	31	140	101	150	89.6	-0.113

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)

```
           Var{e(ij)} = Sigma^2

 Model A2:        Yij = Mu(i) + e(ij)
           Var{e(ij)} = Sigma(i)^2

 Model  R:         Yi = Mu + e(i)
            Var{e(i)} = Sigma^2


Degrees of freedom for Test A1 vs fitted <= 0

                      Likelihoods of Interest

            Model      Log(likelihood)   DF        AIC
              A1       -1947.632025       5    3905.264050
              A2       -1943.411648       8    3902.823297
           fitted      -1948.162584       4    3904.325168
              R        -1962.157799       2    3928.315597

 Test 1:  Does response and/or variances differ among dose levels
          (A2 vs. R)
 Test 2:  Are Variances Homogeneous (A1 vs A2)
 Test 3:  Does the Model for the Mean Fit (A1 vs. fitted)

                    Tests of Interest

   Test    -2*log(Likelihood Ratio)  Test df     p-value

   Test 1             37.4923          6          <.0001
   Test 2             8.44075          3         0.03773
   Test 3             1.06112          0              NA

The p-value for Test 1 is less than .05.  There appears to be a
difference between response and/or variances among the dose levels.
It seems appropriate to model the data

The p-value for Test 2 is less than .05.  Consider running a
non-homogeneous variance model

NA - Degrees of freedom for Test 3 are less than or equal to 0.  The Chi-
Square test for fit is not valid

Benchmark Dose Computation
Specified effect =          0.25

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMC =       0.42196

            BMCL =      0.104163
```

Although Test 3 (mean fit) produced an invalid Chi-Square test (degrees of freedom ≤0), visual inspection of the observed vs expected B cell counts from the Hill model output (Figure A-1) resulted in the determination that the predicted B cell counts adequately reflect the observed values and that the

associated $BMCL_{0.25sd}$ of 0.104163 provides an appropriate point of departure for deriving a chronic-duration inhalation MRL for benzene.

[ ] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 10

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)

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

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

Was a conversion used from intermittent to continuous exposure? The $BMCL_{0.25sd}$ of 0.10 ppm was adjusted from the 8-hour TWA to a continuous exposure concentration ($BMCL_{0.25sdADJ}$) as follows:

$BMCL_{0.25sdADJ} = BMCL_{0.25sd}$ x (8 hours/24 hours) x (6 days/7 days)

Therefore:

$BMCL_{0.25sdADJ}$ = 0.10 ppm x (8 hours/24 hours) x (6 days/7 days)

$BMCL_{0.25sdADJ}$ = 0.03 ppm

Other additional studies or pertinent information that lend support to this MRL: Lan et al. (2004a, 2004b) was selected as the critical study for derivation of a chronic-duration inhalation MRL because it (1) was well designed, (2) provided adequate exposure-response information, (3) employed individual exposure monitoring data collected for up to 16 months prior to blood testing, (4) demonstrated effects that did not appear to be significantly influenced by previous high-level exposures, and (5) included larger numbers of subjects than previous studies (Qu et al. 2002, 2003; Rothman et al. 1996a, 1996b; Ward et al. 1996). In addition, Lan et al. (2004a, 2004b) measured lymphocyte subsets and colony formation from hematopoietic progenitor cells as measures of toxicity.

Previously conducted epidemiology studies provide support to the findings of Lan et al. (2004a). Qu et al. (2002, 2003) compared hematologic values among 105 healthy workers (51 men, 54 women) in industries with a history of benzene usage (Tianjin, China) and 26 age- and gender-matched workers in industries that did not use benzene. Benzene-exposed workers were chosen based on at least 3 years of exposure history. The mean duration of occupational exposure to benzene was 9.7 years (SD=6.2 years). At the time of the study, benzene exposure was monitored by individual organic vapor monitors at 1-week intervals for 4 weeks prior to collection of blood samples for analysis. Measured benzene levels were averaged for each individual to produce a 4-week mean exposure level. Exposure-response relationships were assessed according to ranges of benzene levels (unexposed, >0–5, >5–15, >15–30, and >30 ppm). Benzene hematotoxicity was assessed by mechanical counts of total WBCs, red blood cells (RBCs), and platelets. The WBC differential was hand-counted on a total of 900 cells. Calculations of the numbers of various WBC types were based on total WBCs and differential counts. The mean 4-week benzene level in the control group was 0.004±0.003 ppm. Among all the benzene-exposed workers, the mean 4-week benzene exposure level was 5.2±7.3 ppm. Within the >0–5, >5–15, >15–30, and >30 ppm exposure categories, mean 4-week benzene levels were 2.26±1.35, 8.67±2.44, 19.9±3.1, and

51.8±43.3 ppm, respectively. A significant exposure-related reduction in the numbers of neutrophils (ranging in magnitude from 12% in the 2.26 ppm exposure group to 31% in the 51.8 ppm exposure group) was observed in all four groups of benzene-exposed workers, relative to controls. Significantly reduced numbers of RBCs (approximately 11–16% lower than controls) were also noted in all benzene-exposed groups. Significantly reduced total WBCs were seen in the highest (>30 ppm) exposure group. The study authors identified a subgroup (within the >0–5 ppm exposure group) of 16 women with no measured exposure levels exceeding 0.5 ppm (4-week mean benzene exposure level of 0.14±0.04 ppm) and reported significantly reduced total WBCs, neutrophils, and RBCs in this subgroup as well. However, these results are based on a small number of workers within the larger group and the reduced counts of total WBCs, neutrophils, and RBCs within this subgroup are –much greater in magnitude than those reported for the main (>0–5 ppm) exposure group, rendering the results in this subgroup of questionable value for purposes of risk assessment. Qu et al. (2002, 2003) clearly identified a LOAEL of 2.26 ppm for significantly reduced total WBCs, neutrophils, and RBCs, and provided indication of benzene-induced changes in some hematological values at exposure levels lower than the current industry 8-hour TWA of 1 ppm.

Rothman et al. (1996a, 1996b) performed a cross-sectional study in 1992 on 44 healthy workers (23 males, 21 females) in Chinese (Shanghai) industries with a history of benzene usage and 44 age- and gender-matched workers in industries that did not use benzene. The mean duration of occupational exposure to benzene was 6.3 years (SD=4.4 years). At the time of the study, benzene exposure was monitored by individual organic passive dosimetry badges on 5 separate days during 1 to 2 weeks prior to the collection of blood and urine samples for analysis. Benzene hematotoxicity was assessed by mechanical counts of total WBCs, absolute lymphocytes (ALC), RBCs, and platelets, as well as hemoglobin value and mean corpuscular volume (MCV). The WBC differential was also hand-counted on 100 cells. Abnormal counts were reviewed by hand. Mean (geometric mean of the five exposure samples) 8-hour TWAs for the benzene-exposed workers ranged from 1 to 238 ppm (median 8-hour TWA of 31 ppm). Benzene-exposed workers exhibited statistically significantly reduced numbers of total WBCs, ALC, RBCs, and platelets (approximately 12, 21, 6, and 23% lower, respectively) and significantly increased MCV (approximately 3% higher), relative to unexposed workers. The results were comparable in both men and women. Among the benzene-exposed workers whose mean exposure levels were >31 ppm (median 8-hour TWA of 91.9 ppm; n=22), all measured blood parameters were significantly different from controls; only ALC, RBCs, and platelets were significantly lower in benzene workers with mean exposures of <31 ppm (median 8-hour TWA of 13.6; n=22), compared with controls. In a subgroup of benzene-exposed workers whose measured benzene exposure levels did not exceed 31 ppm on any of the five sampling days (median 8–hour TWA of 7.6 ppm; n=11), significantly reduced ALC (approximately 16% lower than controls) was noted.

In a nested case-control study of a cohort of workers in the Pliofilm production departments of a rubber products manufacturer in Ohio (Ward et al. 1996), incident cases were defined as the first occurrence of a low WBC or RBC count, and matched controls were chosen from those tested within approximately 6 months of the case's blood test date. Hematologic screening data were available for 657 of 1,037 individuals employed at the plant from 1939 through 1976. A total of 21,710 blood test records were identified; the number of blood tests per individual ranged from 1 to 354, but the majority of subjects had five or fewer blood tests. All blood tests were taken from 1940 through 1975, the majority of which were routine hematological screening tests. Benzene exposures were estimated using a job exposure matrix developed by Rinsky et al. (1987). The effects of benzene exposure in the 30, 90, and 180 days prior to the blood test date, as well as cumulative exposure up until the blood test date, were examined using conditional logistic regression. A total of 78 cases and 5,637 controls were included in the WBC analysis and 105 cases and 8,489 controls in the RBC analysis, all of whom had worked only within the rubber hydrochloride departments during the 180 days prior to the selected blood sample date. The maximum daily benzene exposure estimate was 34 ppm. A strong exposure-response relationship

was noted for WBCs, and all of the exposure metrics selected showed a significant relationship with low blood count. A weak positive exposure-response relationship was observed for RBCs, which was significant for the dose metric of cumulative exposure up until the blood test date. The study authors noted that there was no evidence for a threshold for hematologic effects and suggested that exposure to benzene levels <5 ppm may result in hematologic suppression.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Benzene
CAS Numbers: 71-43-2
Date: August 2007
Profile Status: Post Public, Final Draft
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 45
Species: Human

Minimal Risk Level: 0.0005 [x] mg/kg/day [ ] ppm

Reference: Lan Q, Zhang L, Li G, et al. 2004a. Hematotoxicity in workers exposed to low levels of benzene. Science 306:1774-1776.

Experimental design: The chronic-duration oral MRL for benzene is based on route-to-route extrapolation of the results of benchmark dose analysis of a hematological endpoint (B cell count) assessed in 250 workers (approximately two-thirds female) exposed to benzene at two shoe manufacturing facilities in Tianjin, China, and 140 age- and gender-matched workers in clothing manufacturing facilities that did not use benzene. See the MRL worksheet for the chronic-duration inhalation MRL for details of study design.

Effect noted in study and corresponding doses: As described in the MRL worksheet for the chronic-duration inhalation MRL (see also Table A-1), exposure-response relationships were noted for several blood factors. Benzene-induced decreased B cell count was selected as the critical effect for benchmark dose (BMD) modeling because it represented the highest magnitude of effect (i.e., B cell count in the highest exposure group was approximately 36% lower than that of controls). A BMD modeling approach was selected to identify the point of departure because the critical study (Lan et al. 2004a) identified a LOAEL in the absence of a NOAEL.

Dose and end point used for MRL derivation: $BMCL_{0.25sdADJ}$ of 0.014 mg/kg/day for decreased B cell count, resulting from route-to-route extrapolation of the $BMCL_{0.25sdADJ}$ of 0.03 ppm described in the MRL worksheet for the chronic-duration inhalation MRL.

Results of toxicokinetic studies of inhaled benzene in humans (Nomiyama and Nomiyama 1974a; Pekari et al. 1992; Srbova et al. 1950) and inhaled and orally-administered benzene in rats and mice (Sabourin et al. 1987) indicate that absorption of benzene at relatively low levels of exposure is approximately 50% of an inhaled dose and essentially 100% of an oral dose. Based on these assumptions, inhalation data can be used to estimate equivalent oral doses that would be expected to similarly affect the critical targets of benzene toxicity. Therefore, the point of departure for the chronic-duration inhalation MRL for benzene, namely the $BMCL_{0.25sdADJ}$ of 0.03 ppm for decreased B cell counts in benzene-exposed workers (Lan et al. 2004a, 2004b), serves as the point of departure for deriving the chronic-duration oral MRL as well.

The point of departure (in ppm) was converted to mg/m^3 using the molecular weight of 78.11 for benzene and assuming 25 °C and 760 mm Hg:

$BMCL_{0.25sdADJ}$ of 0.03 ppm x 78.11/24.45 = 0.096 mg/m^3

The $BMCL_{0.25sdADJ}$ of 0.096 mg/m^3 for inhaled benzene was converted to an equivalent $BMDL_{0.25sdADJ}$ for ingested benzene using EPA (1988b) human reference values for inhalation rate (20 m^3/day) and body

weight (70 kg) and a factor of 0.5 to adjust for differences in absorption of benzene following inhalation versus oral exposure (50 versus 100%, respectively) as follows:

$BMDL_{0.25sdADJ}$ = $BMCL_{0.25sdADJ}$ of 0.096 mg/m^3 x 20 m^3/day x 0.5 ÷ 70 kg = 0.014 mg/kg/day

[ ] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation: 30

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [x] 10 (for human variability)
[ ] 1 [x] 3 [ ] 10 (for uncertainty in route-to-route extrapolation)

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

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

Was a conversion used from intermittent to continuous exposure? The $BMCL_{0.25sd}$ of 0.10 ppm was adjusted from the 8-hour TWA to a continuous exposure concentration ($BMCL_{0.25sdADJ}$) as follows:

$BMCL_{0.25sdADJ}$ = $BMCL_{0.25sd}$ x (8 hours/24 hours) x (6 days/7 days)

Therefore:

$BMCL_{0.25sdADJ}$ = 0.10 ppm x (8 hours/24 hours) x (6 days/7 days)

$BMCL_{0.25sdADJ}$ = 0.03 ppm

Other additional studies or pertinent information that lend support to this MRL: Results of toxicokinetic studies of inhaled benzene in humans (Nomiyama and Nomiyama 1974a; Pekari et al. 1992; Srbova et al. 1950) and inhaled and orally-administered benzene in rats and mice (Sabourin et al. 1987) indicate that absorption of benzene at relatively low levels of exposure is approximately 50% of an inhaled dose and essentially 100% of an oral dose. Based on these assumptions, inhalation data can be used to estimate equivalent oral doses that would be expected to similarly affect the critical targets of benzene toxicity. See the chronic-duration inhalation MRL worksheet for additional information that supports the selection of the principal study and critical effect for deriving the chronic-duration inhalation MRL.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

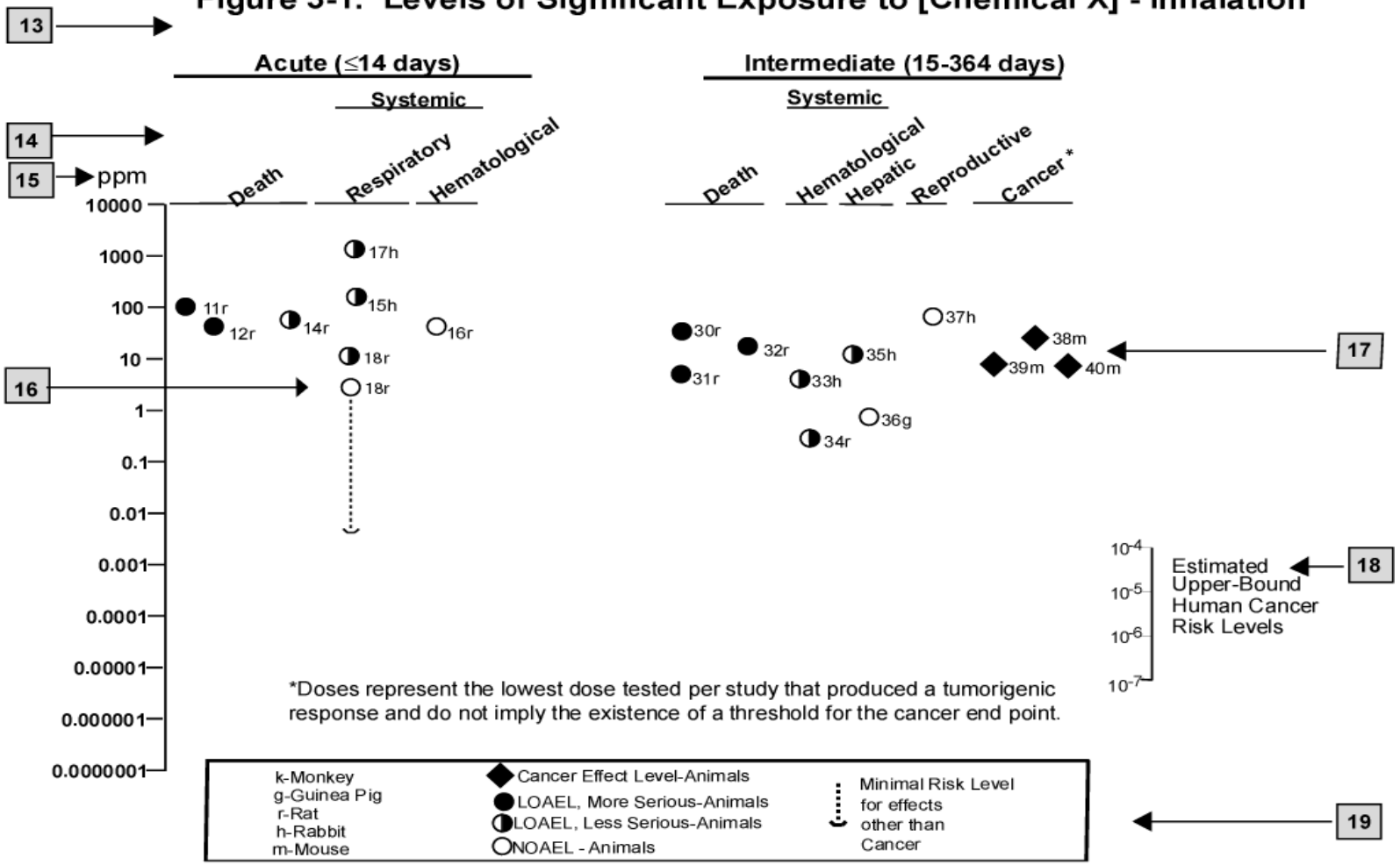
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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