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.

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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: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 1
Species: Human

Minimal Risk Level: [ ] mg/kg/day [2] ppm

Reference: Hollingsworth RL, Rowe VK, Oyen F, et al. 1956. Toxicity of paradichlorobenzene: Determinations on experimental animals and human subjects. AMA Arch Ind Health 14:138-147.

Experimental design: Periodic occupational health examinations were conducted on 58 men who had worked in unspecified industrial operations involving the handling of 1,4-DCB, generally for 8 hours/day and 5 days/week, continually or intermittently for periods of 8 months to 25 years (average 4.75 years). Effects of different workplace exposure levels on eye and nose irritation were summarized. The medical evaluations included careful examination of the eyes, blood cell counts (RBC, WBC, and differential), hemoglobin, hematocrit, mean corpuscular volume, blood urea nitrogen, sedimentation rate, and urinalysis.

Effects noted in study and corresponding doses: Observations in the workers provide information relevant to acute exposures. The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. The odor and irritation properties were considered to be fairly good acute warning properties and were expected to prevent excessive exposures, although the industrial experience indicated that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor. No cataracts or any other lens changes in the eyes, or effects on the clinical indices were attributable to exposure.

Dose and end point used for MRL derivation:

[15] NOAEL [] LOAEL

As discussed above, eye and nose irritation are critical effects of acute inhalation exposure to 1,4-DCB in humans. Because odor detection is a warning property expected to prevent irritation caused by 1,4-DCB, the highest level at which an odor was detected that was simultaneously without irritant effects, 30 ppm, was designated a minimal LOAEL for irritation for the purposes of derivation of the MRL; the 15 ppm level was therefore designated a NOAEL for irritant effects.

Uncertainty Factors used in MRL derivation:

[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? No.

Other additional studies or pertinent information that lend support to this MRL: A limited amount of information is available on the toxicity of inhaled 1,4-DCB in humans. Case reports of people who inhaled 1,4-DCB provide indications that the liver and nervous system are systemic targets of inhalation toxicity in humans, but are limited by lack of adequate quantitative exposure information and/or verification that 1,4-DCB was the only factor associated with the effects (Cotter 1953; Miyai et al. 1988; Reygagne et al. 1992).

Information on effects of acute-duration inhalation exposure to 1,4-DCB in animals is available from short-term systemic toxicity studies in rats and guinea pigs (Hollingsworth et al. 1956), a male reproduction study rats (Anderson and Hodge 1976), and developmental toxicity studies in rats and rabbits (Hayes et al. 1985; Hodge et al. 1977). In the systemic toxicity study, five rats of each sex and five guinea pigs of each sex were exposed to 175 ppm of 1,4-DCB for 7 hours/day, 5 days/week for 16 days (Hollingsworth et al. 1956). Mild histological effects of interstitial edema, congestion, and alveolar hemorrhage were observed in the lungs of male rats and female guinea pigs. The experimental design and report of this study have a number of deficiencies, such that reported observations provide only qualitative evidence of exposure-related respiratory effects. In the reproduction study (a dominant lethal test), a NOAEL of 450 ppm was identified for reproductive performance in male mice that were exposed for 6 hours/day for 5 days prior to weekly mating with unexposed females for 8 weeks (Anderson and Hodge 1976). No maternal or developmental toxicity occurred in rats that were exposed to 75–500 ppm for 6 hours/day on days 6–15 of gestation (Hodge et al. 1977), indicating that the highest NOAEL for reproductive effects in rats is 500 ppm. A developmental study in which rabbits were exposed to 100–800 ppm for 6 hours/day on gestation days 6–18 found evidence of fetotoxicity (a minor variation of the circulatory system) only at 800 ppm, which was also maternally toxic as shown by body weight loss early in gestation (Hayes et al. 1985), indicating that 800 ppm is a LOAEL for maternal and developmental effects in rabbits.

The lung appears to be a target of concern for inhaled 1,4-DCB in rats and guinea pigs exposed to 173 ppm (Hollingsworth et al. 1956), because the only effects observed in the reproductive and developmental studies were indications of maternal and fetotoxicity in rabbits at a much higher levels of 800 ppm (Hayes et al. 1985). Support for the respiratory tract as a sensitive target for 1,4-DCB inhalation in animals is provided by the induction of nasal lesions in rats intermittently exposed to levels as low as 75 ppm for 104 weeks in the study used to derive the chronic inhalation MRL for 1,4-DCB (Japan Bioassay Research Center 1995). Additionally, the animal data are consistent with the human experience, indicating that occupational exposure to 1,4-DCB causes painful nose and eye irritation in the range of 50–160 ppm (Hollingsworth et al. 1956).

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

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CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 14
Species: Rat

Minimal Risk Level: [ ] mg/kg/day [0.2] ppm

References: Aiso A, Arito H, Nishizawa T, et al. 2005a. Thirteen-week inhalation toxicity of *p*-dichlorobenzene in mice and rats. J Occup Health 47:249-260.

Tyl RW, Neeper-Bradley TL. 1989. Paradichlorobenzene: Two generation reproductive study of inhaled paradichlorobenzene in Sprague-Dawley (CD) rats. Laboratory Project 86-81-90605. Washington, DC: Chemical Manufacturers Association, Chlorobenzene Producers Association.

Experimental design and effects noted (Aiso et al. 2005a): This is a systemic toxicity study in which groups of 10 male and 10 female F344 rats and 10 male and 10 female BDF_1 mice were chamber-exposed to 1,4-DCB vapor (>99.9% pure) at target concentrations of 0, 25, 55, 120, 270, or 600 ppm for 6 hours/day, 5 days/week for 13 weeks. Deviations in mean observed concentrations from the target concentrations were <9.6%. End points evaluated during the study included clinical signs (daily) and body weight and food consumption (weekly). End points evaluated at the end of the 13-week exposure period included hematology (RBC, Hb, Hct, MCV, MCH), blood biochemistry (total protein, albumin, total cholesterol, triglyceride, phospholipid, AST, ALT, AP, BUN, creatine), organ weights, and histopathology. The histological examinations were comprehensive and included the nasal cavity, in accordance with OECD test guidelines for a 90-day inhalation study (Aiso 2005a; OECD 1981).

There were no exposure-related effects on survival, clinical signs, or body weight gain in the rats. Hematological changes suggestive of microcytic anemia occurred in male rats, including significantly decreased RBC count and hemoglobin concentration at ≥120 ppm, hematocrit at ≥270 ppm, and MCV and MCH at 600 ppm. Serum biochemical changes included significant increases in total protein in both sexes at 600 ppm, albumin in females at ≥270 ppm and males at 600 ppm, and total cholesterol and phospholipid in males at ≥270 ppm and females at 600 ppm, and significant decreases in triglycerides in males at 600 ppm, AST in both sexes at 600 ppm, and ALT and AP in males at ≥270 ppm. Organ weight changes included >10% increases in absolute and relative weights of liver in males at ≥270 ppm and females at 600 ppm, kidneys in males at ≥270 ppm, and spleen in males at 600 ppm. Histological effects included significantly increased incidences of liver centrilobular hepatocellular hypertrophy in male rats at 600 ppm (incidences in the control to high dose groups were 0/10, 0/10, 0/10, 0/10, 3/10, and 10/10), and kidney lesions indicative of $\alpha_{2\mu}$-globulin nephropathy (hyaline droplets, granular casts, tubular cell necrosis, cytoplasmic basophila, and papillary mineralization) in male rats at ≥270 ppm. There were no histopathological changes in hematopoietic tissues (e.g., increased extramedullary hematopoiesis or hemosiderosis in the spleen), leading the investigators to suggest the possibility that the anemia in the male rats was secondary to $\alpha_{2\mu}$-globulin nephropathy-related effects on erythropoietin synthesis in the renal tubules.

There were no exposure-related effects on survival, clinical signs, or body weight gain in the mice. Organ weight changes in the mice included >10% increases in liver weight in males at ≥270 ppm (relative) and

600 ppm (absolute) and females at 600 ppm (absolute and relative); relative liver weights were 9.7, 9.7, 10.1, 23.9, and 62.6% higher than controls in the low- to high-dose males. There were no significant hematological changes in either sex. Serum ALT levels were significantly increased in males at ≥270 ppm (18.2, 9.1, 18.2, 54.5, and 164% higher than controls in the low- to high-dose groups). Other serum biochemical changes included significant increases in ALT in females at 600 ppm, AST in males at 600 ppm, and total cholesterol and total protein in both sexes at 600 ppm. Histological examinations showed significantly ($p \leq 0.01$) increased incidences of centrilobular hepatocellular hypertrophy at in male mice at ≥270 ppm and female mice at 600 ppm; incidences in the control to high dose groups were 0/10, 0/10, 0/10, 0/10, 10/10, and 10/10 in the males and 0/10, 0/10, 0/10, 0/10, 0/10, and 10/10 in the females. Affected hepatocytes were characterized by cell enlargement, varying nuclear size and shape, and coarse chromatin and inclusion bodies in the nucleus; the severity of these lesions was rated as slight at 270 ppm (males) and moderate at 600 ppm (both sexes). The moderate hepatocellular hypertrophy in the 600 ppm male mice was accompanied by single cell necrosis (1/10) and focal liver necrosis (2/10).

The lowest effect level is 270 ppm based on the kidney and hematological effects in male rats and liver effects in rats and mice. The kidney and hematological effects are consistent with $\alpha_{2\mu}$-globulin nephropathy, which is specific to male rats and not relevant to humans. The mice were more sensitive to the liver effects of 1,4-DCB than the rats because the only hepatic change in the 270 ppm rats was increased liver weight, whereas hepatocellular hypertrophy and increased serum ALT occurred in addition to increased liver weight in the 270 ppm mice. Additionally, at the next highest tested level of 600 ppm, the mice had nuclear changes and evidence of necrosis in the hypertrophic hepatocytes, and increased serum AST as well as ALT, whereas none of these indicators of hepatocellular damage occurred in the rats. Based on increased relative liver weight (>10%) in both species and histological and serum ALT changes in the mice, this study identified a NOAEL of 120 ppm and a LOAEL of 270 ppm for hepatic effects. The identification of the liver as a critical target of 1,4-DCB is supported by findings of increased liver weight and serum liver enzymes, as well as histopathologic liver lesions in dogs administered 1,4-DCB orally for up to 1 year (Naylor and Stout 1996).

Experimental design and effects noted (Tyl and Neeper-Bradley 1989): This is a two-generation study in which groups of 28 Sprague-Dawley rats of each sex were exposed to actual mean 1,4-DCB concentrations of 0, 66, 211, and 538 ppm for 6 hours/day, 7 days/week. Additional groups of 10 females were similarly exposed for 10 weeks in a satellite study. The animals in the main study were paired within groups for a 3-week mating period to produce the F_1 generation. Main study males that did not successfully mate in the first 10 days of the mating period were paired with the satellite females for 10 days. Main study females that did not successfully mate during the first 10 days of the mating period were paired with proven males for the remaining 11 days of the mating period. Exposures of the main study F_0 females were continued throughout the mating period and the first 19 days of gestation, discontinued from gestation day 20 through postnatal day 4, and then resumed until sacrifice at weaning on postnatal day 28. Exposures of the satellite F_0 females were continued through mating until sacrifice on gestation day 15. Exposures of the F_0 males continued until sacrificed at the end of the study and satellite mating periods (F_0 males were exposed for a total of 15 weeks). Groups of 28 F_1 weanlings/sex and satellite groups of 10 F_1 female weanlings were exposed for 11 weeks and mated as described above to produce the F_2 generation. Additionally, 20 F_1 weanlings/sex from the control and high exposure groups served as recovery animals that were observed without exposure for 5 weeks prior to sacrifice. Complete necropsies were performed on all F_0 and F_1 adult (parental) animals, F_1 recovery animals, F_1 weanlings not used in the rest of the study, and F_2 weanlings, and histology was evaluated in the F_0 and F_1 parental animals. Histological examinations were conducted on the liver and kidneys in all groups and on selected other tissues (pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, prostate, and tissues with gross lesions) in the control and high exposure groups. The kidney evaluation included examination for the presence of $\alpha 2_{\mu}$ droplets. Additional end points evaluated in the parental generations included clinical observations, mortality, body weight, and food consumption. Mating and

fertility indices were determined for F_0 and F_1 males and females, and gestational, live birth, postnatal survival (4-, 7-, 14-, 21-, and 28-day), and lactation indices were determined for the F_1 and F_2 litters.

There were no effects on reproductive parameters in either generation, although systemic toxicity occurred at all dose levels in F_0 and F_1 adult rats. Hyaline droplet nephropathy was found in F_0 and F_1 adult males at ≥66 ppm. Manifestations of this male rat-specific renal syndrome included $\alpha_{2\mu}$-globulin accumulation and increased kidney weights at ≥66 ppm, and other characteristic histological changes at 538 ppm. Body weights and weight gain were significantly reduced in F_0 and F_1 adult males and F_1 adult females during the pre-breed exposure periods at 538 ppm. Absolute liver weights were increased in F_0 males by 6, 16, and 38% in the 66, 211, and 538 ppm groups, respectively; the differences were statistically significantly different from control in the 211 and 538 ppm groups. In F_0 females, absolute liver weights were increased by 9 and 31% at 211 and 538 ppm, respectively, but statistical significance was achieved only at 538 ppm. Similar changes were seen in relative liver weights of the F_0 generation, with respective increases of 5, 14, and 52% in the 66, 211, and 538 ppm males and 4, 9, and 31% in the 66, 211, and 538 ppm females; all groups of treated males, and the 211 and 538 ppm female groups, were statistically significantly different from controls. Relative liver weights were also significantly increased in F_1 adult males at ≥211 ppm and F_1 adult females at 538 ppm. Hepatocellular hypertrophy was observed in the livers of F_0 and F_1 males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. Other effects also occurred in the F_0 and F_1 males and females at 538 ppm, indicating that there was a consistent pattern of adult toxicity at the high exposure level, including reduced food consumption and increased incidences of clinical signs (e.g., tremors, unkempt appearance, urine stains, salivation, and nasal and ocular discharges); these effects only sporadically occurred at 211 ppm. Other effects at 538 ppm included reduced gestational and lactational body weight gain, and postnatal toxicity, as evidenced by increased number of stillborn pups, reduced pup body weights, and reduced postnatal survival in F_1 and/or F_2 litters. This study identified a (1) a NOAEL of 66 ppm and LOAEL of 211 ppm for increased (>10% above controls) relative liver weight in adult rats, and (2) a serious LOAEL of 538 ppm for systemic toxicity (central nervous system and other clinical signs) in adult rats and developmental toxicity (increased stillbirths and perinatal mortality) in their offspring. The identification of increased liver weight as a critical effect of 1,4-DCB toxicity is supported by findings of increased liver weight and serum liver enzyme levels and histopathologic liver lesions following repeated oral exposure (Naylor and Stout 1996).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMCL

As discussed below, a $BMCL_{1sd}$ of 92.45 ppm for increased liver weight in rats was used as the point of departure for the MRL.

Benchmark dose (BMD) analysis was conducted using the Tyl and Neeper-Bradley (1989) data for relative liver weight in adult male rats (Table A-1) and the Aiso et al. (2005a) serum ALT data in male rats (Table A-2). A benchmark response (BMR) of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. BMD analysis of the relative liver weight data from the Aiso et al. (2005a) study is precluded by insufficient information (standard deviations were not reported). Incidences of hepatocellular hypertrophy in the male mice of the Aiso et al. (2005a) study were not subjected to BMD analysis because the response was observed in 0% of control, 25, 55, and 120 ppm animals and in 100% of the 270 and 600 ppm animals. The F_1 and F_2 postnatal survival data (Tyl and Neeper-Bradley 1989) were not subjected to BMD analysis because the 211 ppm exposure level represents a NOAEL and the next higher exposure level (538 ppm) represents a frank effect level (FEL) for 4-day survival (12.6 and 28.1% reductions in 4-day survival of F_1 and F_2 pups, respectively) and clinical signs in F_0 males and females.

Table A-1. Relative Liver Weight Data for F_0 Male Rats Exposed to 1,4-Dichlorobenzene Vapors 6 Hours/Day for 15 Weeks

	Mean measured exposure concentration (ppm)			
	0	66	211	538
Group size	27	28	28	28
Relative liver weight (%)	3.465±0.2328[a]	3.631±0.2080[b]	3.945±0.2592[c]	5.271±0.2474[c]

[a]Mean ± standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Tyl and Neeper-Bradley 1989

Table A-2. Serum ALT Data for Male Rats Exposed to1,4-Dichlorobenzene Vapors 6 Hours/Day, 5 Days/Week for 13 Weeks

	Mean measured exposure concentration (ppm)					
	0	25	55	120	270	600
Group size	10	10	10	10	10	10
Serum ALT (IU/L)[a]	11±2	13±8	12±4	13±4	17±3[b]	29±6[c]

[a]Mean ± standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Aiso et al. 2005a

All appropriate continuous-variable (linear, polynomial, power) models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the serum ALT data from the male rats of the Aiso et al. (2005a) study (the Hill model was excluded due to an insufficient number of exposure groups). An assumption of constant variance resulted in a p-value <0.0005 for the test of constant variance and a non-homogeneous variance assumption was suggested. However, the assumption of non-homogeneous variance resulted in inadequately modeled variance (p-value <0.0005) and BMD analysis of the serum ALT data from the male rats of the Aiso et al. (2005a) study was considered an inadequate method for selecting a point of departure for deriving an intermediate-duration inhalation MRL for 1,4-DCB.

Available continuous-variable models were also fit to the Tyl and Neeper-Bradley (1989) data for changes in liver weight. A BMR of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. The simplest model (linear) for continuous data was initially fit to the data; constant variance was selected (Table A-3). The model output indicated that constant variance was appropriate, but inadequate model mean fit was obtained (p-value <0.01). The more complex (polynomial, power, Hill) models were also fit to the liver weight data. The Hill model provided inadequate mean fit due to an insufficient number of dose groups (4, including controls), which resulted in insufficient (0) degrees of freedom. The 2-degree polynomial provided adequate mean fit and the power model provided marginally adequate mean fit as indicated by the p-values for mean fit (Table A-3). The 2-degree polynomial model was the best fitting model (the adequate model with the lowest Akaike's Information Criteria [AIC]), predicting a BMC_{1sd} and $BMCL_{1sd}$

(lower 95% confidence limit on the BMC_{1sd}) of 119.91 and 92.45 ppm, respectively (Table A-3). A plot of observed and predicted relative liver weight from the 2-degree polynomial model is shown in Figure A-1.

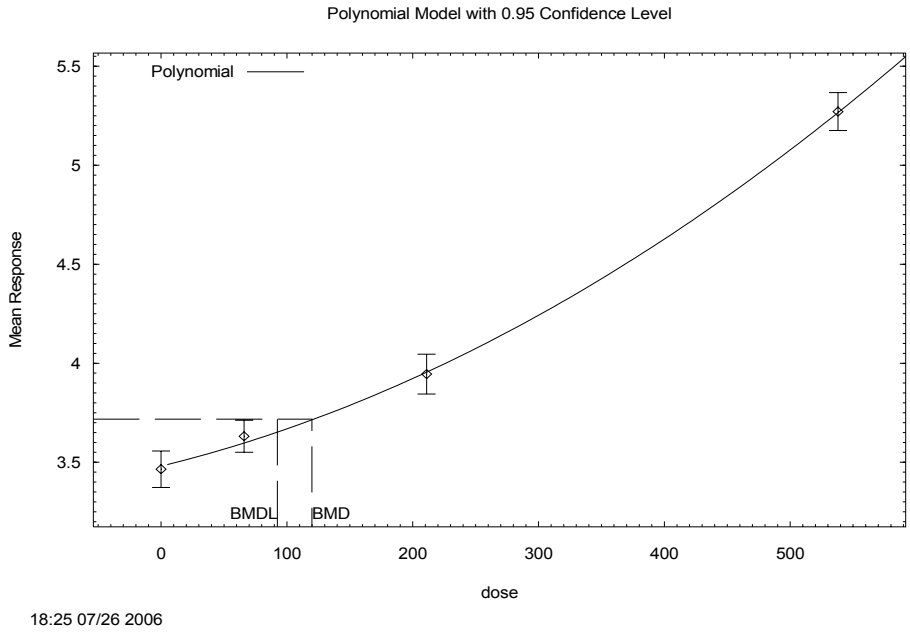
Table A-3. Model Predictions for Relative Liver Weight in F_0 Male Rats Exposed to 1,4-Dichlorobenzene Vapors 6 Hours/Day for 15 Weeks

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMC_{1sd} (ppm)	$BMCL_{1sd}$ (ppm)
Linear[b, c]	0.6877	0.00026	NA	NA	NA
2-Degree polynomial[b,c]	0.6877	0.3926	-205.3345	119.907	92.4533
Power[b]	0.9241	0.09954	-202.3525	129.587	100.477

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative

BMC_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation from the control mean; $BMCL_{1sd}$ = lower confidence limit (95%) on the BMC_{1sd}; NA = not applicable because model failed a goodness-of-fit test

Figure A-1. Observed Liver Weights in Adult Male Rats Exposed to 1,4-Dichlorobenzene for 15 Weeks and Predicted Relative Liver Weights by the 2-Degree Polynomial Model*



*BMD = BMC; BMDL=BMCL; BMC and BMCL (in ppm) are associated with a 1 standard deviation from the control mean.

The $BMCL_{1sd}$ of 92.45 ppm was duration-adjusted to 23 ppm, converted to a human equivalent concentration (HEC) of 23 ppm, and divided by an uncertainty factor of 100 to derive an MRL of 0.2 ppm.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Although the rat BMCL was adjusted to a HEC (see below), an uncertainty factor of 10 for extrapolation from animals to humans was still applied, because the HEC calculation was based on an assumption of equivalent blood-gas partition coefficients, and not on actual data.

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: 1,4-DCB exhibited the effects outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the MRL. The HEC for extrarespiratory effects produced by a category 3 gas is calculated by multiplying the duration-adjusted $BMCL_{1sd}$ ($BMCL_{1sd\ ADJ}$, see below) by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats and humans. Using a default value of 1 for the ratio of partition coefficients, the $BMCL_{1sd\ HEC}$ becomes 23 ppm:

$$BMCL_{1sd\ HEC} = (BMCL_{1sd\ ADJ}) \times [(H_{b/g})_{RAT} / (H_{b/g})_{HUMAN}],$$
$$= 23 \text{ ppm} \times [1] = 23 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? The $BMCL_{1sd}$ of 92 ppm was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMCL_{1sd\ ADJ} = (BMCL_{1sd}) \text{ (hours/24 hours) (days/7 days)}$$
$$= (92.45 \text{ ppm}) \text{ (6 hours/24 hours) (7 days/7 days)}$$
$$= 23 \text{ ppm}$$

Other additional studies or pertinent information that lend support to this MRL: Supporting information on hepatic effects of intermediate-duration inhalation exposure to 1,4-DCB are available from a multispecies subchronic toxicity study in which rats, mice, guinea pigs, rabbits, and monkeys were exposed to 96 or 158 ppm for 7 hours/day, 5 days/week for 5–7 months (Hollingsworth et al. 1956). Some of these animals were also similarly exposed to 341 ppm for 6 months (rats and guinea pigs) or 798 ppm for 23–69 exposures (rats, guinea pigs, and rabbits). The experiments with rabbits and monkeys exposed to levels of 96 or 158 ppm are limited by small numbers of animals (1–2/group). Hepatic effects included increased relative liver weight and slight histological alterations in rats at 158 ppm (not observed at 96 ppm), and more severe histopathology (e.g., cloudy swelling and necrosis) in guinea pigs at 341 ppm, and in rats, guinea pigs, and rabbits at 798 ppm. Other findings in the animals exposed to 798 ppm included eye irritation and frank signs of neurotoxicity (e.g., marked tremors). The hepatic histological changes observed in rats at 158 ppm (cloudy swelling, congestion, or granular degeneration) were considered of questionable significance and were not reported at 358 ppm, indicating that neither 158 nor 358 ppm is a reliable LOAEL for liver pathology in rats in this study. The hepatic histological effects observed in the guinea pigs at 341 ppm appear have been more severe (fatty degeneration, focal necrosis, slight cirrhosis) than in rats, but only occurred in some of the animals (number not reported). Although this information suggests that 341 ppm is a LOAEL for liver histopathology in guinea pigs, confidence in this effect level is low due to imprecise and brief qualitative reporting of the results (a

general limitation of the study). The 798 ppm exposure concentration is a reliable LOAEL because this level clearly caused both liver histopathology (e.g., cloudy swelling and central necrosis) and overt signs of toxicity (e.g., marked tremors, eye irritation, and unconsciousness) in all three species.

A chronic inhalation study was conducted in which rats and mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks (Aiso et al. 2005b). Effects in the rats included nasal lesions at ≥75 ppm and increased liver weight at 300 ppm, and effects in the mice included increased liver weight and hepatocellular hypertrophy at 300 ppm. The 75 ppm NOAEL and 300 ppm LOAEL for liver effects in the chronic study are consistent with the 120 ppm NOAEL and 211 ppm LOAEL for liver effects in the intermediate-duration studies (Aiso et al. 2005a; Tyl and Neeper-Bradley 1989). The 75 ppm LOAEL for nasal lesions in rats indicates that these tissues are more sensitive than the liver following chronic exposure, and the nasal lesions were used as the basis for the chronic inhalation MRL for 1,4-DCB. Because nasal lesions were not found in the 13-week study, it appears that the lesions are late-developing effects of chronic exposure. The lack of nasal lesions in the 13-week study therefore indicates that these are not critical effects of intermediate-duration exposure.

The NOAEL/LOAEL approach to MRL derivation results in the same MRL as the 0.2 ppm value derived using the BMD approach. The 13-week study (Aiso et al. 2005a) and two-generation study (Tyl and Neeper-Bradley 1989) are consistent in identifying the liver as the most sensitive target of intermediate duration inhalation of 1,4-DCB and showing that hepatic effects increased in severity with increasing level of exposure. The 13-week study (Aiso et al. 2005a) identified a hepatic NOAEL of 120 ppm and a LOAEL of 270 ppm in rats (increased liver weight) and mice (increased liver weight, hepatocellular hypertrophy, and serum ALT). The two-generation study identified a hepatic NOAEL of 66 ppm and a LOAEL of 211 ppm in rats (increased liver weight). The 120 ppm NOAEL is the highest hepatic NOAEL below the lowest hepatic LOAEL of 211 ppm, indicating that it is an appropriate basis for MRL derivation using the NOAEL/LOAEL approach. Using the NOAEL of 120 ppm for liver effects in male mice (the more sensitive species and sex), the NOAEL was duration-adjusted for the intermittent experimental exposure, as follows:

$$\begin{aligned} NOAEL_{ADJ} &= \text{(NOAEL) (hours/24 hours) (days/7 days)} \\ &= \text{(120 ppm) (6/24) (5/7)} \\ &= \text{21.4 ppm} \end{aligned}$$

1,4-DCB exhibited the effects outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the human equivalent concentration (HEC). The HEC for extra respiratory effects produced by a category 3 gas is calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994k). $H_{b/g}$ values were not available for 1,4-DCB in rats, mice and humans. Using a default value of 1 for the ratio of partition coefficients, the $NOAEL_{HEC}$ is 21.4 ppm, calculated as follows:

$$\begin{aligned} NOAEL_{HEC} &= (NOAEL_{ADJ}) \times [(H_{b/g})_{MOUSE} / (H_{b/g})_{HUMAN}], \\ &= \text{21.4. ppm x [1] = 21.4 ppm} \end{aligned}$$

The $NOAEL_{HEC}$ was divided by the uncertainty factor of 100 to derive an MRL of 0.2 ppm.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 32
Species: Rat

Minimal Risk Level: [ ] mg/kg/day [0.01] ppm

References: Aiso S, Takeuchi T, Arito H, et al. 2005b. Carcinogenicity and chronic toxicity in mice and rats exposed by inhalation to *para*-dichlorobenzene for two years. J Vet Med Sci 67(10):1019-1029.

Japan Bioassay Research Center. 1995. Toxicology and carcinogenesis studies of p-dichlorobenzene in 344/DuCrj rats and Crj:BDF1 mice. Two-year inhalation studies. Japan Industrial Safety and Health Association. Study carried under contract with the Ministry of Labour of Japan.

Experimental design: Groups of 50 male and female F344/DuCrj rats and 50 male and female Crj:BDF_1 mice were exposed to 1,4-DCB in target concentrations of 0, 20, 75, or 300 ppm for 6 hours/day, 5 days/week for 104 weeks. Study end points included clinical signs and mortality, body weight (weekly for the first 13 weeks, and subsequently every 4 weeks), and hematology, blood biochemistry, and urinalysis indices (evaluated at end of study). Selected organ weight measurements (liver, kidneys, heart, lungs, spleen, adrenal, brain, testis, ovary) and comprehensive gross pathology and histology evaluations were performed on all animals at the end of the study or at time of unscheduled death. No interim pathology examinations were performed.

Effects noted in study and corresponding doses: For the rats, the actual mean chamber concentrations were 0, 19.8, 74.8, or 298.4 ppm over the duration of the study. The number of rats surviving to scheduled termination was significantly ($p<0.05$) reduced at 300 ppm in males. Survival in the male rats was noticeably lower than controls beginning at approximately study week 80, and overall survival at 0, 20, 75, and 300 ppm was 66% (33/50), 68% (34/50), 58% (29/50), and 36% (18/50), respectively. There were no exposure-related decreases in survival in the female rats, or effects on growth or food consumption in either sex. Changes in various hematological and blood biochemical indices (mean cell volume, total cholesterol, phospholipids, blood urea nitrogen, creatinine, and calcium in males; total protein, total bilirubin, blood urea nitrogen, and potassium in females) occurred at 300 ppm (Japan Bioassay Research Center 1995), but a lack of both numerical data and statistical analysis precludes interpretations of significance for these end points. Absolute and relative liver weights in both sexes and kidney weights in males were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal epithelia and kidneys. The nasal lesions mainly included increased incidences of eosinophilic changes (globules) in the olfactory epithelium (moderate or greater severity) in males at 300 ppm and females at ≥75 ppm. Incidences of this lesion at 0, 20, 75, and 300 ppm were 1/50, 2/50, 2/50, and 7/50 in males, and 27/50, 29/50, 39/50, and 47/50 in females. The increases were statistically significant ($p\leq0.05$, Fisher's Exact Test performed by ATSDR) at ≥75 ppm in females and 300 ppm in males, and there was a trend of increasing response with increasing dose in both sexes (Cochran-Armitage test, performed by ATSDR). Other nasal lesions that were significantly increased at 300 ppm were eosinophilic globules in the respiratory epithelium (11/50, 10/50, 14/50, 38/50) and respiratory metaplasia in the nasal gland (5/50, 4/50, 4/50, 33/50) in females at 300 ppm. Kidney lesions were increased only in male rats at 300 ppm and included significantly increased incidences of

mineralization of the renal papilla (0/50, 1/50, 0/50, 41/50) and in hyperplasia of the urothelium (7/50, 8/50, 13/50, 32/50).

For the mice, the actual mean chamber concentrations were 0, 19.9, 74.8, or 298.3 ppm over the duration of the study. Survival was significantly reduced in male mice at 300 ppm (due to an increase in liver tumor deaths), but comparable to controls in the females. Terminal body weight was significantly reduced at 300 ppm in males (11.5% less than controls, beginning at study week 80). Changes in various hematological and blood biochemical indices (total cholesterol, SGOT, SGPT, LDH, and AP in both sexes; platelet numbers, total protein, albumin, total cholesterol, blood urea nitrogen, and calcium in females) occurred at 300 ppm (Japan Bioassay Research Center 1995), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these end points. Absolute and relative liver and kidney weights in both sexes were significantly increased at 300 ppm. Additional findings included histopathological changes in the nasal cavity, liver, and testes. The nasal lesions included significantly increased incidences of respiratory metaplasia in the nasal gland (moderate severity) in males at 75 ppm (9/49, 12/49, 18/50, 11/49) and olfactory epithelium (slight severity) in males at 75 ppm (23/49, 30/49, 37/50, 22/49) and females at 300 ppm (7/50, 6/50, 2/49, 20/50); the effects in the males were not dose-related (i.e., incidences were increased at 75 ppm but not at 300 ppm). The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 300 ppm (0/49, 0/49, 0/50, 34/49). Incidences of liver tumors were also increased at 300 ppm; these included hepatocellular carcinoma in males (12/49, 17/49, 16/50, 38/49) and females (2/50, 4/50, 2/49, 41/50), hepatocellular adenoma in females (2/50, 10/50, 6/49, 20/50), hepatoblastoma in males (0/49, 2/49, 0/50, 8/49) and females (0/50, 0/50, 0/49, 6/50), and histiocytic sarcoma in males (0/49, 3/49, 1/50, 6/49). Testicular mineralization was significantly increased in males at ≥75 ppm (27/49, 35/49, 42/50, 41/49) (Japan Bioassay Research Center 1995). The testicular mineralization was not considered to be a toxicologically significant effect (Aiso 2006) because (1) no signs of testicular toxicity were observed in mice exposed for 13 weeks (Aiso et al. 2005a), and (2) it was confined to the testicular capsules and testicular blood vessels and not observed in the testicular parenchyma, indicating that it is a finding commonly observed in aged mice independent of exposure to 1,4-DCB (Aiso 2006).

The results of this study indicate that moderate or severe eosinophilic changes in the nasal olfactory epithelium in female rats is the most sensitive toxic effect in the most sensitive species and sex. The NOAEL and LOAEL for these nasal lesions are 19.8 and 74.8 ppm, respectively.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMCL

As discussed below, a $BMCL_{10}$ of 9.51 ppm for increased incidences of nasal lesions in female rats is used as the point of departure for the MRL.

BMD analysis was conducted using the incidences for eosinophilic changes of moderate or greater severity in the nasal olfactory epithelium in female rats and the actual exposure concentrations. The data that were modeled are shown in Table A-4. Data for other end points were not modeled because the effects occurred at higher concentrations (nasal lesions and hepatocellular hypertrophy in mice, kidney lesions in rats) or were not toxicologically significant (testicular mineralization in mice). All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the female rat nasal lesion incidence data. A 10% extra risk above the control incidence was selected as the BMR in the absence of a biological rationale for using an alternative BMR. As assessed by the chi-square goodness-of-fit statistic, all models provided adequate fits to the data (the quantal quadratic model was marginally adequate based on a chi-square p-value of 0.09 rather than the conventionally acceptable p-value of ≥0.1). The gamma, multistage, quantal linear, and Weibull models provided identical fit and were judged the

best-fitting models based on the lowest AIC value (Table A-5). These models each provided a benchmark concentration (BMC_{10}) of 14.08 ppm and lower 95% confidence limit ($BMCL_{10}$) of 9.51 ppm. A representative plot of the observed and predicted incidences of nasal lesions from the quantal linear model output is shown in Figure A-2. The $BMCL_{10}$ of 9.51 ppm was duration-adjusted to 1.70 ppm, converted to a HEC of 0.27 ppm, and divided by an uncertainty factor of 30 to derive an MRL of 0.01 ppm.

Table A-4. Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Exposure concentration (ppm)	0	19.8	74.8	298.4
Nasal olfactory epithelial lesions (incidence)[a]	27/50[b]	29/50	39/50[c]	47/50[c]

[a]Lesions of moderate or greater severity.
[b]Significant trend of increasing response with increasing dose (Cochran-Armitage Test, performed by ATSDR).
[c]Significantly (p≤0.05) different from control value (Fisher's Exact Test performed by ATSDR).

Source: Aiso et al. 2005b

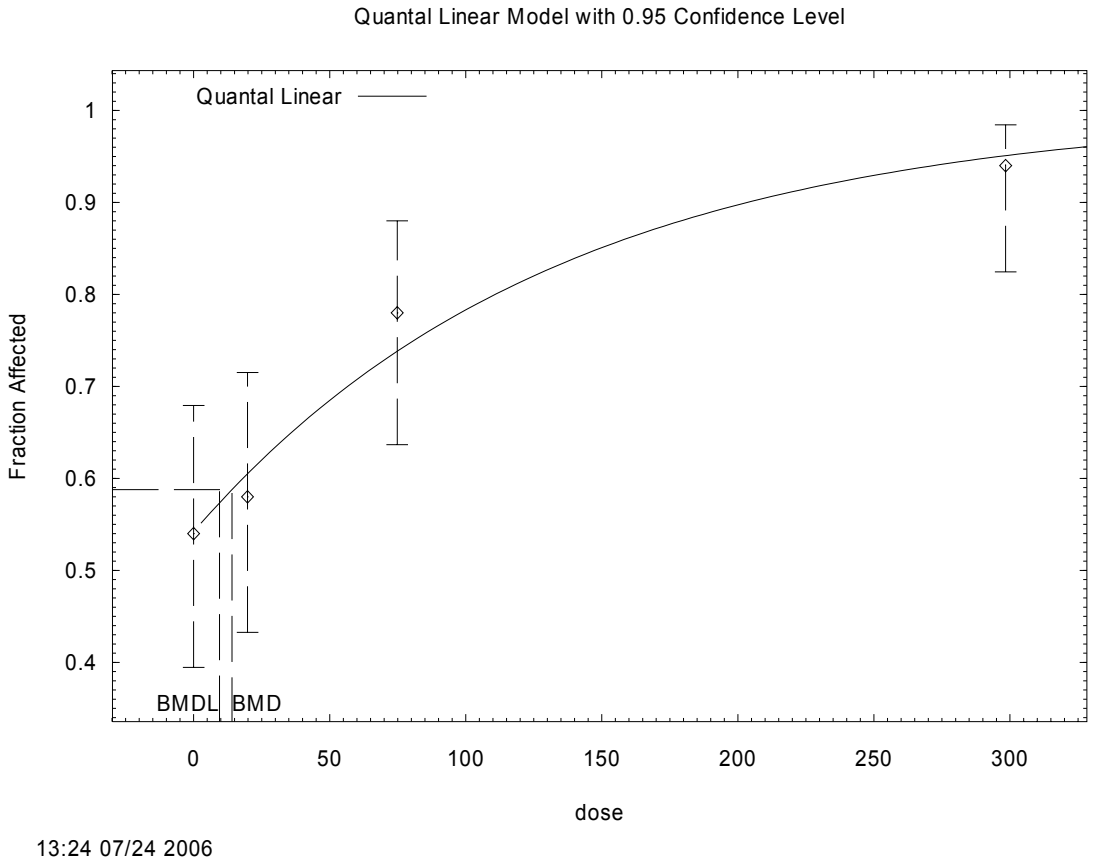
Table A-5. Modeling Results for Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Model	Chi-square p-value[a]	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[b]	0.70	217.13	14.08	9.51
Logistic	0.51	217.79	19.43	13.90
Log-logistic[c]	0.74	218.52	15.45	4.12
Multi-stage[d]	0.70	217.13	14.08	9.51
Probit	0.42	218.21	22.17	16.70
Log-probit[c]	0.74	218.52	16.09	3.20
Quantal linear	0.70	217.13	14.08	9.51
Quantal quadratic	0.09	221.36	67.38	53.07
Weibull[b]	0.70	217.13	14.08	9.51

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

AIC = Akaike's Information Criteria; BMC_{10} = benchmark dose associated with a 10% extra risk; $BMCL_{10}$ = lower confidence limit (95%) on the benchmark dose

Figure A-2. Observed and Predicted Incidences of Nasal Lesions in Female Rats Exposed to 1,4-Dichlorobenzene for 104 Weeks*



*BMD = BMC; BMDL = BMCL; BMC and BMCL (in ppm) are associated with a 10% extra risk. The quantal linear model plot in this figure is identical to the plots produced by the gamma, multistage, and Weibull models.

Uncertainty Factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans
[X] 10 for human variability

A 3-fold uncertainty factor was used instead of a default 10-fold factor to extrapolate from rats to humans because the dosimetry adjustment (i.e., calculation of the human equivalent exposure for time and concentration [HEC]) addresses one of the two areas of uncertainty encompassed in an interspecies extrapolation factor. The dosimetric adjustment addresses the pharmacokinetic component of the extrapolation factor, but the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: For the nasal olfactory epithelium changes in female rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region for purposes of calculating the HEC. Using EPA (1988, 1994b) reference values, the regional gas deposition ratio was calculated as follows (EPA 1994a):

$RGDR_{ET}$ = $[(V_E/SA_{ET})_A/(V_E/SA_{ET})_H]$
= $(0.24\ m^3/day/15cm^2)/(20\ m^3/day/200cm^2)$
= 0.16

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The HEC was calculated by multiplying the rat $BMCL_{10\ ADJ}$ by the $RGDR_{ET}$ to yield a $BMCL_{10\ HEC}$ of 0.27 ppm, as follows:

$BMCL_{10\ HEC}$ = $BMCL_{10\ ADJ}$ x $RGDR_{ET}$
= 1.70 ppm x 0.16
= 0.27 ppm

Was a conversion used from intermittent to continuous exposure? The animal $BMCL_{10}$ value of 15.34 ppm was duration-adjusted for intermittent experimental exposure, as follows:

$BMCL_{10\ ADJ}$ = $(BMCL_{10})$ (hours/24 hours) (days/7 days)
= (9.51 ppm) (6 hours/24 hours) (5 days/7 days)
= 1.70 ppm

Other additional studies or pertinent information that lend support to this MRL: The only other information on the chronic inhalation toxicity of 1,4-DCB in animals is available from another study in rats and mice (Riley et al. 1980a, 1980b). In this study, rats of both sexes and female mice were exposed to 75 or 500 ppm of 1,4-DCB for 5 hours/day, 5 days/week for up to 76 weeks (rats) or 57 weeks (mice), followed by 32 weeks (rats) or 18–19 weeks (mice) without exposure. There were no exposure-related histopathological changes in the nasal cavity or other tissues in either species. Liver and kidney weights were increased in rats of both sexes at 500 ppm, but the toxicological significance is questionable due to the negative histopathology findings and the lack of related clinical chemistry effects. Evaluation of the mouse data is limited by reporting insufficiencies in the available summary of the study.

A limited amount of information is available on the long-term toxicity of inhaled 1,4-DCB in humans. Periodic occupational health examinations of workers who were exposed to 1,4-DCB for an average of 4.75 years (range 8 months to 25 years) showed no changes in standard blood and urine indices (Hollingsworth et al. 1956). The odor was found to be faint at 15–30 ppm and strong at 30–60 ppm. Painful irritation of the eyes and nose was usually experienced at 50–80 ppm, although the irritation threshold was higher (80–160 ppm) in workers acclimated to exposure. Concentrations above 160 ppm caused severe irritation and were considered intolerable to people not adapted to it. Occasional examination of the eyes showed no cataracts or any other lens changes. The odor and irritation properties were considered to be fairly good warning properties that should prevent excessive exposures, although the industrial experience indicated that it is possible for people to become sufficiently acclimated to tolerate high concentrations of the vapor. The data from this study are inadequate for chronic MRL derivation due to poor characterization of long-term exposure levels, insufficient investigation of systemic health end points, reporting and other study deficiencies. Although the available human information is insufficient for chronic MRL derivation, the human eye and nose irritation data are consistent with the nasal effects observed in the chronically exposed animals.

The NOAEL/LOAEL approach to MRL derivation results in an MRL of 0.02 ppm, similar to the 0.01 ppm value based on BMD analysis. Using the NOAEL of 19.8 ppm for moderate or severe changes

in the nasal olfactory epithelium in rats (Aiso et al. 2005b), the NOAEL was duration-adjusted for intermittent experimental exposure, as follows:

$NOAEL_{ADJ}$ = (NOAEL) (hours/24 hours) (days/7 days)
= (19.8 ppm) (6 hours/24 hours) (5 days/7 days)
= 3.54 ppm

A HEC was calculated using EPA (1994a) inhalation dosimetric adjustment methodology. For the olfactory epithelium changes in rats, 1,4-DCB was treated as a category 1 gas with effects in the extrathoracic region. Using EPA (1988, 1994b) reference values, the regional gas deposition ratio was calculated as follows:

$RGDR_{ET} = [(V_E/SA_{ET})_A/(V_E/SA_{ET})_H]$
$= (0.24\ m^3/day/15cm^2)/(20\ m^3/day/200cm^2)$
$= 0.16$

where: $RGDR_{ET}$ = regional gas deposition ratio in the extrathoracic region
V_E = minute volume in rats $(V_E)_A$ or humans $(V_E)_H$
SA_{ET} = extrathoracic surface area in rats $(SA_{ET})_A$ or humans $(SA_{ET})_H$

The rat $NOAEL_{ADJ}$ was multiplied by the $RGDR_{ET}$ to yield a $NOAEL_{HEC}$ of 0.57 ppm (3.54 ppm x 0.16), and the $NOAEL_{HEC}$ was divided by the uncertainty factor of 30 to derive an MRL of 0.02 ppm.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzene (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 11
Species: Rat

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

Reference: Robinson M, Bercz JP, Ringhand HP, et al. 1991. Ten and ninety-day toxicity studies of 1,2-dichlorobenzene administered by oral gavage to Sprague-Dawley rats. Drug Chem Toxicol 14(1&2):83-112.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,2-DCB in corn oil by gavage in doses of 0, 37.5, 75, 150, or 300 mg/kg/day for 10 consecutive days. The doses were selected on the basis of a reported rat oral LD_{50} of 500 mg/kg. End points evaluated during the study included clinical signs, body weight, and food and water consumption. Evaluations at the end of the exposure period included hematology (five indices), serum chemistry (nine indices including AST, ALT, LDH, cholesterol, BUN, and creatinine), and selected organ weights (brain, liver, spleen, lungs, thymus, kidneys, adrenal glands, heart, and testes or ovaries). Histological examinations were performed on various tissues including liver, kidneys, urinary bladder, heart, skin, muscle, bone, respiratory tract (nasal cavity with turbinates, lungs), nervous system (brain, sciatic nerve), immunological (spleen, thymus, lymph nodes), gastrointestinal (duodenum, ileum, jejunum, salivary gland, colon, cecum, rectum), endocrine (adrenal glands, pancreas), and reproductive (testes, seminal vesicles, prostate, ovaries) in the high-dose and control groups. Target organs identified in the high-dose groups were also histologically evaluated at the lower dose levels.

Effects noted in study and corresponding doses: No clinical signs or effects on survival were observed. Body weight gain was significantly reduced in the male rats at 300 mg/kg/day (final body weights were 10.9% lower than controls), but not in females, and there were no exposure-related changes in food consumption in either sex. Statistically significant changes in organ weights predominantly occurred at 300 mg/kg/day, including significantly decreased absolute spleen weight in both sexes, and decreased absolute heart, kidney, thymus, and testes weights in males. Liver weight (relative and absolute) was significantly increased in females at ≥150 mg/kg/day and in males at 300 mg/kg/day; compared to controls in the low- to high-dose females, absolute liver weights were 1.8, 9.0, 20.5, and 29.0% increased and relative liver weights were 6.8, 7.6, 21.7, and 34.5% increased. Clinical chemistry findings included significantly increased serum ALT in both sexes at 300 mg/kg/day and serum phosphorus in females at ≥150 mg/kg/day. Serum cholesterol was significantly increased in females at ≥37.5 mg/kg/day, but the toxicological significance is unclear because values were similar at all dose levels and showed no dose-response. Histopathological findings were limited to the liver and included necrosis that was slight in severity and significantly ($p=0.04$) increased in males at 300 mg/kg/day (4/10 compared to 0/10 in controls; incidences in the other dose groups were not reported, although the study authors indicated that target organs in the high-dose groups were histologically evaluated at the lower dose levels. Incidences of other hepatic lesions were not significantly increased, but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized by varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). Because incidences of histopathologic liver lesions were not reported for females, it is presumed that incidences in

the control and high-dose females were 0/10 and that the lower female dose groups were not assessed for liver lesions. This study identified a NOAEL of 75 mg/kg/day and LOAEL of 150 mg/kg/day for increased liver weight in female rats, as well as a LOAEL of 300 mg/kg/day for liver necrosis in male rats.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 67.73 mg/kg/day for increased liver weight in female rats is used as the point of departure for the MRL.

BMD analysis was conducted using the rat absolute liver weight data (Robinson et al. 1991) shown in Table A-6. The liver lesion data were not subjected to BMD analysis because incidences of liver necrosis were only reported for control and high-dose rats. Serum liver enzyme (ALT, AST, LDH) data were not subjected to BMD analysis because a statistically significant increase was noted only for serum ALT in the high-dose group of male rats and the magnitude of the increase (50% higher than the control serum ALT level) is not considered to be adverse.

Table A-6. Absolute Liver Weights in Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days

		Dose (mg/kg/day)				
Effect	Sex	0	37.5	75	150	300
Absolute liver weight (g)	M	9.8±0.70[a] n=10	10.30±0.94 n=10	9.90±0.62 n=10	10.21±1.29 n=10	11.00±0.83[b] n=10
	F	6.00±0.45 n=10	6.11±0.33 n=10	6.54±0.70 n=10	7.23±0.62[b] n=10	7.74±0.41[b] n=10

[a]Mean ± standard deviation
[b]Significantly (p≤0.05) different from control value

Source: Robinson et al. 1991

All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the absolute liver weight data from male and female rats. One standard deviation increase from the control mean value was selected as the BMR in the absence of a biological rationale for using an alternative BMR. The modeling results are shown in Table A-7. Constant variance was assumed; the assumption was considered appropriate based on p-values >0.1 for the test of homogeneous variance. The linear, 2-degree polynomial, power, and Hill models provided adequate mean fit to the male rat liver weight data, as determined by p-values >0.1 for the test of mean fit. The linear model was determined to the best-fitting model (lowest AIC among all adequate model outputs) for the male rat liver weight data and provided a BMD_{1sd} of 249.04 mg/kg/day and a $BMDL_{1sd}$ of 158.55 mg/kg/day. For the female liver weight data, the linear and Hill models provided adequate mean fit (p-values >0.1). The linear model was the best-fitting model (lowest AIC) for the female rat liver weight data and provided a BMD_{1sd} of 84.67 mg/kg/day and a $BMDL_{1sd}$ of 67.73 mg/kg/day. Among the best-fitting model results for absolute liver weight in the male and female rats, the lowest (linear model-generated) $BMDL_{1sd}$ of 67.73 mg/kg/day for increased absolute liver weight in female rats is selected as the point of departure for deriving the MRL. The $BMDL_{1sd}$ of 67.73 mg/kg/day was divided by an uncertainty factor of 100 to derive an MRL of 0.7 mg/kg/day.

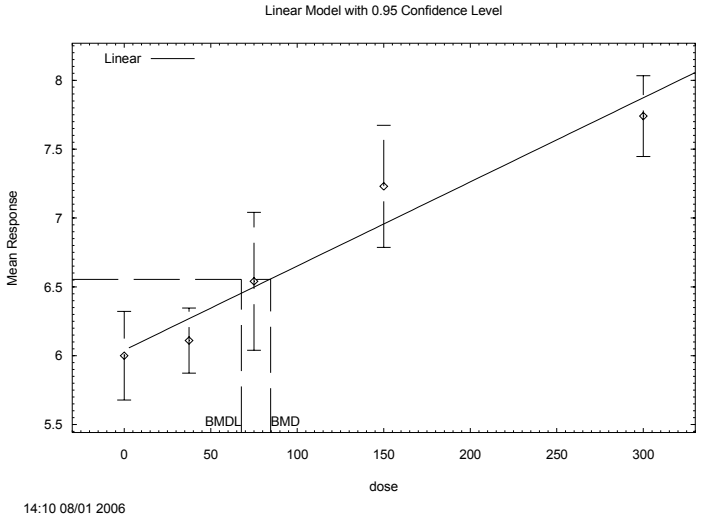
Table A-7. Model Predictions for Increased Absolute Liver Weight in Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Males					
Linear[b]	0.15	0.48	41.40	249.04	158.55
Polynomial[b,c,d]	0.15	0.38	42.87	274.93	164.78
Power[b,e]	0.15	0.38	44.86	281.79	164.87
Hill[b,f]	0.15	0.17	46.80	180.01	No value
Females					
Linear[b]	0.12	0.19	-11.85	84.67	67.73
Polynomial[b,c,d,]	0.12	0.09	-11.85	84.67	67.73
Power[b,e]	0.12	0.09	-7.85	84.67	67.73
Hill[b,f]	0.12	0.84	-10.55	71.51	43.18

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Constant variance assumed
[c]Restriction = non-negative
[d]2-degree polynomial
[e]Restrict power >=1
[f]Restrict n>1
[g]Non-homogeneous variance assumed

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose associated with one standard deviation increase above control mean; BMDL = lower confidence limit (95%) on the benchmark dose

Figure A-3. Observed and Predicted Mean Absolute Liver Weight in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days*



*The BMD and BMDL (in mg/kg/day) represent a 1 standard deviation increase in mean absolute liver weight from the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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

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

Other additional studies or pertinent information that lend support to this MRL: Information on effects of acute oral exposure to sublethal doses of 1,2-DCB essentially consists of findings in three systemic toxicity studies in rats and mice and one developmental toxicity study in rats (NTP 1985; Rimington and Ziegler 1963; Robinson et al. 1991; Ruddick et al. 1983). These studies administered the compound by gavage and collectively identify the liver as the most sensitive target. Severe liver damage, characterized by intense necrosis and fatty changes as well as porphyria, occurred in rats administered 455 mg/kg/day for 15 consecutive days (Rimington and Ziegler 1963). Rats that were exposed to 300 mg/kg/day for 10 consecutive days had hepatic effects that included necrosis and increased serum ALT (Robinson et al. 1991). Hepatocellular degeneration and necrosis occurred in mice that were exposed to 250 or 500 mg/kg/day for 14 consecutive days (NTP 1985). The 15-day rat and 14-day mouse studies are limited by small numbers of animals (3–5 per dose) and lack of a NOAEL due a single dose level (Rimington and Ziegler 1963) or lack of histopathology evaluations at doses lower than the LOAEL (NTP 1985). The 10-day study (Robinson et al. 1991) is the most appropriate basis for MRL derivation because it is well designed, included four dose levels, and provides dose-response data for several hepatic end points.

The NOAEL/LOAEL approach to MRL derivation results in an MRL similar to the 0.7 mg/kg/day value based on BMD analysis. Using the 75 mg/kg/day NOAEL for increased liver weight (Robinson et al. 1991) and the uncertainty factor of 100, the NOAEL/LOAEL approach yields an MRL of 0.8 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzenes (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 17
Species: Rat

Minimal Risk Level: [0.6] mg/kg/day [ ] ppm

Reference: NTP. 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 255. NIH Publication No. 86-2511.

Experimental design: Groups of 10 male and 10 female F344/N rats and 10 male and 10 female $B6C3F_1$ mice were administered 1,2-DCB (>99% pure) in corn oil by gavage in doses of 0, 30, 60, 125, 250, or 500 mg/kg on 5 days/week for 13 weeks. Evaluations included clinical signs, body weight, food consumption, hematology, clinical chemistry, urine volume, urine uroporphyrins and coproporphyrins, liver porphyrins, organ weights, and necropsies in all groups of animals. Complete histological examinations were performed on all control and high-dose animals; histology exams in lower dose groups were limited to liver, kidneys and thymus at 125 and 250 mg/kg/day.

Effects noted in study and corresponding doses: Effects in the rats included necrosis of individual hepatocytes at ≥250 mg/kg/day and centrilobular degeneration at 500 mg/kg/day; total incidences of these lesions at 0, 125, 250, and 500 mg/kg/day were 0/10, 1/10, 4/9, and 8/10 in males, and 0/10, 3/10, 5/10, and 7/8 in females. Relative liver weights were significantly increased at 125, 250, and 500 mg/kg/day in the males (8, 17, and 45% higher than controls) and females (8, 15, and 30%); increased relative liver weights were not seen at lower doses in either sex. There were no increases in serum levels of liver enzymes [ALT, AP, or GGPT] at any dose in either sex. Serum cholesterol was significantly increased in males at ≥30 mg/kg/day (50.0, 17.6, 26.5, 70.6, and 109% higher than controls in the low- to high-dose groups, not significant at 60 mg/kg/day) and females at ≥125 mg/kg/day (12.2, 12.2, 32.6, 26.5, and 51.0%). Although increases in serum cholesterol were observed at levels as low as 30 mg/kg/day, the toxicological significance is unclear because there was no clear dose-response unless the increase at 30 mg/kg/day is considered to be outlying. Urinary concentrations of uroporphyrin and coproporphyrin were 3–5 times higher than controls in the 500 mg/kg/day males and females, but this increase was not considered indicative of porphyria because total porphyrin concentration in the liver was not altered at any dose level and no pigmentation indicative of porphyria was observed by ultraviolet light at necropsy. The increases in relative liver weight and liver lesions seen in both sexes at 125 mg/kg/day are believed to represent the beginning of adverse hepatic effects, and are thus designated a minimal LOAEL for this study. The NOAEL is therefore 60 mg/kg/day.

In the mice, no compound-related histopathological changes were observed in either sex at 0 and 125 mg/kg/day, or in females at 250 mg/kg/day. Lesions that were significantly increased included necrosis of individual hepatocytes, hepatocellular degeneration and/or pigment deposition in 4/10 males at 250 mg/kg/day, and centrilobular necrosis, necrosis of individual hepatocytes, and/or hepatocellular degeneration in 9/10 males and 9/10 females at 500 mg/kg/day. Relative liver weights were significantly increased at 500 mg/kg/day in both sexes, but there were no exposure-related changes in serum levels of ALT, AP, or GGPT in either sex at any dose (no other clinical chemistry indices were examined in the

mice). Based on the liver lesion data, the NOAEL and LOAEL in mice are 125 and 250 mg/kg/day, respectively.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 89.27 mg/kg/day for increased relative liver weight in female rats is used as the point of departure for the MRL.

Benchmark dose analysis was conducted using the male and female rat and male mouse liver lesion incidence data summarized in Table A-8. Dichotomous models available in the EPA Benchmark Dose Software were fit to data for incidences of liver lesions (single cell necrosis, centrilobular necrosis, and/or hepatocellular degeneration) in male and female rats (combined) and male mice. Because there were no apparent differences in sensitivity to 1,2-DCB among the male and female rats, the liver lesion data were combined to increase the statistical power for BMD analysis. For each data set (combined incidences in male and female rats and incidences in male mice), the Chi-square p-value and AIC were used to select the best fitting model from which BMDs and their lower 95% confidence limits (BMDLs) were calculated, using a BMR of 10% extra risk.

Table A-8. Incidences of Liver Lesions in Rats and Mice Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

Lesions: Individual cell or focal necrosis; centrilobular degeneration in high-dose group	Dose (mg/kg/day)					
	0	30	60	125	250	500
Male rat	0/10	ND	ND	1/10	4/9[a]	8/10[a]
Female rat	0/10	ND	ND	3/10	5/10[a]	7/8[a]
Combined (male and female)	0/20	ND	ND	4/20[a]	9/19[b]	15/18[b]
Male mouse	0/10	ND	ND	0/10	4/10[a]	9/10[a]

[a]Significantly ($p<0.05$) different from control; Fisher Exact Test performed by ATSDR
[b]Significantly ($p<0.01$) different from control; Fisher Exact Test performed by ATSDR

ND = no histological examinations conducted in this group

Source: NTP 1985

All models provided adequate fit to liver lesion data for male and female rats combined (Table A-9). The best-fitting model (lowest AIC) was the quantal quadratic model, which provided a BMD_{10} of 108.71 mg/kg/day and a $BMDL_{10}$ of 92.08 mg/kg/day. The log-probit model was determined to be the best-fitting model for the male mouse data and provided a BMD_{10} of 176.05 mg/kg/day and $BMDL_{10}$ of 114.58 mg/kg/day.

Table A-9. BMD Model Results of Incidence Data for Liver Lesions in Male and Female Rats (Combined) and Male Mice Exposed to 1,2-Dichlorobenzene for 13 Weeks

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Male and female rats combined				
Gamma[b]	0.99	66.53	81.08	31.38
Logistic	0.34	69.78	112.08	81.57
Log Logistic[c]	0.94	66.64	89.36	39.14
Multi-stage[d]	0.99	66.55	66.22	31.31
Probit	0.38	69.33	106.79	78.36
Log-probit[c]	0.94	66.64	92.42	54.15
Quantal-linear	0.67	66.20	38.18	27.93
Quantal-quadratic	0.64	66.02	108.71	92.08
Weibull	0.99	66.52	75.28	31.39
Male mice				
Gamma[b]	0.75	24.78	172.36	102.08
Logistic	0.44	26.24	168.53	106.72
Log-logistic[c]	0.81	24.62	175.35	110.25
Multi-stage[d]	0.48	24.57	116.66	63.82
Probit	0.48	25.93	167.39	102.39
Log-probit[c]	0.86	24.42	176.05	114.58
Quantal-linear	0.14	30.41	44.73	28.59
Quantal-quadratic	0.69	24.57	116.66	91.67
Weibull	0.61	25.46	158.84	86.28

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas >=0; lowest degree polynomial (2-degree) with an adequate fit

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose based on a benchmark response of 10%; $BMDL_{10}$ = lower confidence limit (95%) on the BMD_{10}

BMD analysis was also conducted using the relative liver weight data for male and female rats shown in Table A-10). Continuous variable models in the EPA Benchmark Dose Software were fit to the liver weight data, and one standard deviation from the control mean was selected as the BMR in the absence of a biological rationale for using a different BMR. For the male rat relative liver weight data, results of model runs using constant variance indicated that non-homogeneous variance was more appropriate. However, selection of non-homogeneous variance resulted in inadequate mean fits (p-value <0.04) from the linear, polynomial, and power models, and the Hill model would not generate an output. For the relative liver weight data of the female rats, constant variance was appropriate (p-value >0.1) and adequate mean fits were obtained from the linear, polynomial, and power models (Table A-11). The Hill model would not generate an output for the female relative liver weight data. Among the adequate mean fits, the linear model provided the lowest AIC and was therefore selected as the best-fitting model for the

female rat relative liver weight data (Table A-11, Figure A-4), which resulted in a BMD_{1sd} of 108.15 mg/kg/day and a $BMDL_{1sd}$ of 89.27 mg/kg/day.

Table A-10. Relative Liver Weight Data for Male and Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

	Mean measured exposure concentration (ppm)					
	0	30	60	125	250	500
Males						
Group size	9	9	10	9	9	10
Relative liver weight[a]	3.18	3.28	3.10	3.43[b]	3.72[b]	4.61[b]
Standard deviation	0.20	0.22	0.15	0.22	0.29	0.47
Females						
Group size	10	10	10	10	10	8
Relative liver weight[a]	2.90	2.98	2.92	3.13[b]	3.33[b]	3.78[b]
Standard deviation	0.20	0.15	0.16	0.20	0.18	0.30

[a]Mean value
[b]Significantly different ($p<0.05$) from control group

Source: NTP 1985

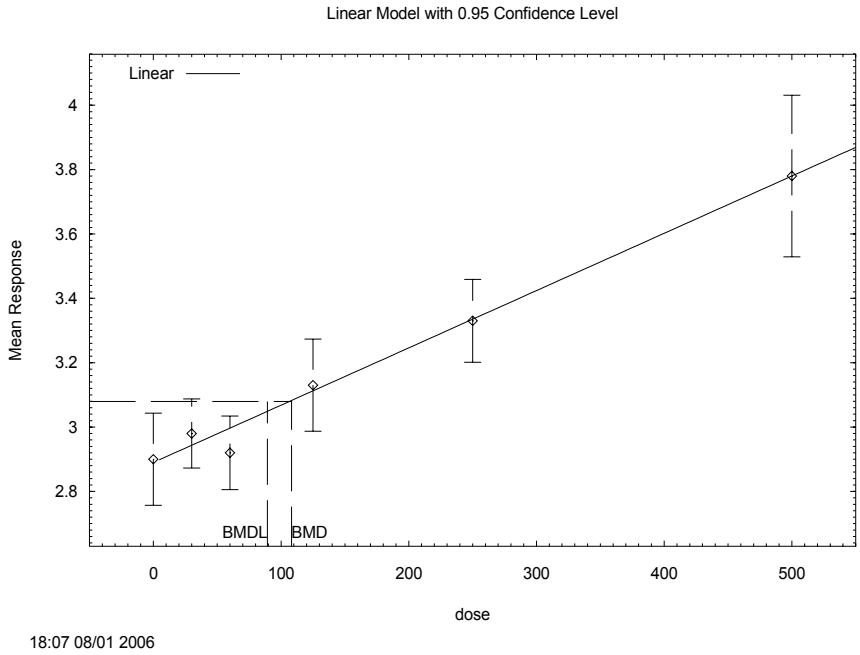
Table A-11. Model Predictions for Relative Liver Weight in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (ppm)	$BMDL_{1sd}$ (ppm)
Linear[b]	0.338	0.719	-129.0910	108.15	89.27
2-Degree polynomial[b,c]	0.338	0.559	-127.1169	112.34	89.34
Power[b,d]	0.338	0.5679	-125.1600	116.96	89.47

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Power restricted to >=1

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation from the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}

Figure A-4. Observed and Predicted Mean Relative Liver Weights in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 1 standard deviation increase above the control mean

The $BMDL_{1sd}$ of 89.27 mg/kg/day from the best-fitting modeling results of the female rat relative liver weight data is lower than the $BMDL_{10}$ of 92.08 mg/kg/day from the best-fitting modeling results of liver lesion incidences in the male and female rats combined and the $BMDL_{10}$ of 114.58 mg/kg/day from the best-fitting model results of liver lesion incidences in the male mice. Therefore, the $BMDL_{1sd}$ of 89.27 mg/kg/day for increased relative liver weight in the female rats is selected as the point of departure for the MRL. The $BMDL_{1sd}$ of 89.27 mg/kg/day was duration-adjusted to 63.76 mg/kg/day and divided by an uncertainty factor of 100 to yield an MRL of 0.6 mg/kg/day.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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 $BMDL_{1sd}$ of 89.27 mg/kg/day was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (\text{days}/7\ \text{days})$$
$$= (89.27\ \text{mg/kg/day})\ (5\ \text{days}/7\ \text{days})$$
$$= 63.76\ \text{mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL: Information on effects of intermediate-duration oral exposure to 1,2-DCB are available from three intermediate studies in rats and mice identifying the liver as the most sensitive target of toxicity (Hollingsworth et al. 1958; NTP 1985; Robinson et al. 1991). Incidences of degenerative liver lesions were significantly increased in rats and mice exposed to ≥250 mg/kg/day, 5 days/week for 13 weeks (NTP 1985), 376 mg/kg/day, 5 days/week for 192 days (Hollingsworth et al. 1958; NTP 1985), and 400 mg/kg/day for 90 consecutive days (Robinson et al. 1991). Necrotic lesions also occurred in several rats at 125 mg/kg/day (1/10 males, 3/10 females) in the NTP (1985) study, but the increase was not statistically significant. Other hepatic findings in rats exposed to lower doses (125–188 mg/kg/day for ≥13 weeks) in these studies included small increases in relative liver weight and serum levels of ALT, cholesterol, and serum protein, and decreases in serum triglycerides. Increased serum ALT is an inconsistent finding because it was induced in rats exposed to ≥100 mg/kg/day for 90 days (Robinson et al. 1991), but not in rats exposed to ≥125 mg/kg/day for 13 weeks (NTP 1985). Additionally, the increase in serum ALT was not dose-related, and serum levels of other liver-associated enzymes were not increased in either the Robinson et al. (1991) study (AST, LDH, and AP) or the NTP (1985) study (AP and gamma-glutamyltranspeptidase [GGTP]). The lowest LOAEL is 125 mg/kg/day, which is a minimal LOAEL for increased liver weight in rats in the NTP (1985) study; the corresponding NOAEL is 60 mg/kg/day.

The NOAEL/LOAEL approach to MRL derivation results in a lower MRL than the 0.6 mg/kg/day value based on benchmark dose analysis. Using the 60 mg/kg/day NOAEL for increased liver weight in rats (NTP 1985), the NOAEL is duration-adjusted to 42.9 mg/kg/day (60 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichlorobenzene (1,2-DCB)
CAS Numbers: 95-50-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 31
Species: Mouse

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

Reference: NTP. 1985. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (o-dichlorobenzene) (CAS No. 95-50-1) in F344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 255. NIH Publication No. 86-2511.

Experimental design: Groups of 50 male and 50 female F344/N rats and 50 male and 50 female $B6C3F_1$ mice were administered 1,2-DCB (>99% pure) in corn oil by gavage in doses of 0, 60, or 120 mg/kg on 5 days/week for 103 weeks. Evaluations included clinical signs, body weight, and gross observations in all groups of animals. Complete histological examinations were performed on all animals, and included evaluations of at least 30 tissues.

Effects noted in study and corresponding doses: Survival was significantly reduced in high-dose male rats, relative to control male rats, but not in the low-dose group or in any group of female rats. Mean body weights of high-dose male rats were slightly, but not statistically significantly, lower than those of controls throughout the study; the mean body weights of low-dose males were comparable to those of controls, and exposed female rats had higher body weights than controls. No changes in clinical signs were reported for either sex of rats. No increases in gross observations were reported on necropsy, and no changes in nonneoplastic lesions were seen in the liver, kidney, bone marrow, spleen, thymus, or other organs or tissues in exposed rats.

In the mice, no statistically significant differences in survival were seen in either sex at any dose level. Mean body weights were similar to controls for all treated groups of male and female mice. In male mice, there was a dose-related increase in the incidence of renal tubular regeneration (controls: 8/48; low dose: 12/50; high dose: 17/49); the increase was statistically significant (Fisher's Exact Test, performed by ATSDR) in the high-dose group. No other increases were observed in nonneoplastic lesions of the liver, bone marrow, spleen, or any other evaluated organ or tissue.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{10}$ of 43.04 mg/kg/day for increased incidences of renal tubular regeneration in male mice is used as the point of departure for the MRL.

BMD analysis was conducted using the kidney lesion incidence data summarized in Table A-12. All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to the male mouse incidence data for renal tubule regeneration. A 10% extra risk above the control incidence was selected as the BMR in the absence of a biological rationale for using an alternative BMR. The modeling results are shown in Table A-13. The gamma, log-logistic, and Weibull models outputs failed to provide Chi-

square p-values for goodness of fit statistic (Chi-square = 0; degrees of freedom = 0) and were therefore not considered for selection of a point of departure. The other models (logistic, multistage, probit, log-probit, quantal-linear, and quantal-quadratic) provided adequate fits to the data (Chi-square p-values ≥0.1). The logistic model was the best-fitting model for the renal tubule regeneration incidence data, based on the lowest AIC, and provided a BMD_{10} of 62.96 mg/kg/day and a $BMDL_{10}$ of 43.04 mg/kg/day (Table A-13, Figure A-5). The $BMDL_{10}$ of 43.04 mg/kg/day was duration-adjusted to 30.74 mg/kg/day and divided by an uncertainty factor of 100 to yield an MRL of 0.3 mg/kg/day.

Table A-12. Incidences of Kidney Lesions in Male Mice Orally Exposed to 1,2-Dichlorobenzene for 103 Weeks

	Dose (mg/kg/day)		
Lesion: Regeneration of kidney tubule cells	0	60	120
Incidence/group size	8/48	12/50	17/49[a]

[a]Significantly (p<0.05) different from control; Fisher Exact Test performed by ATSDR

Source: NTP 1985

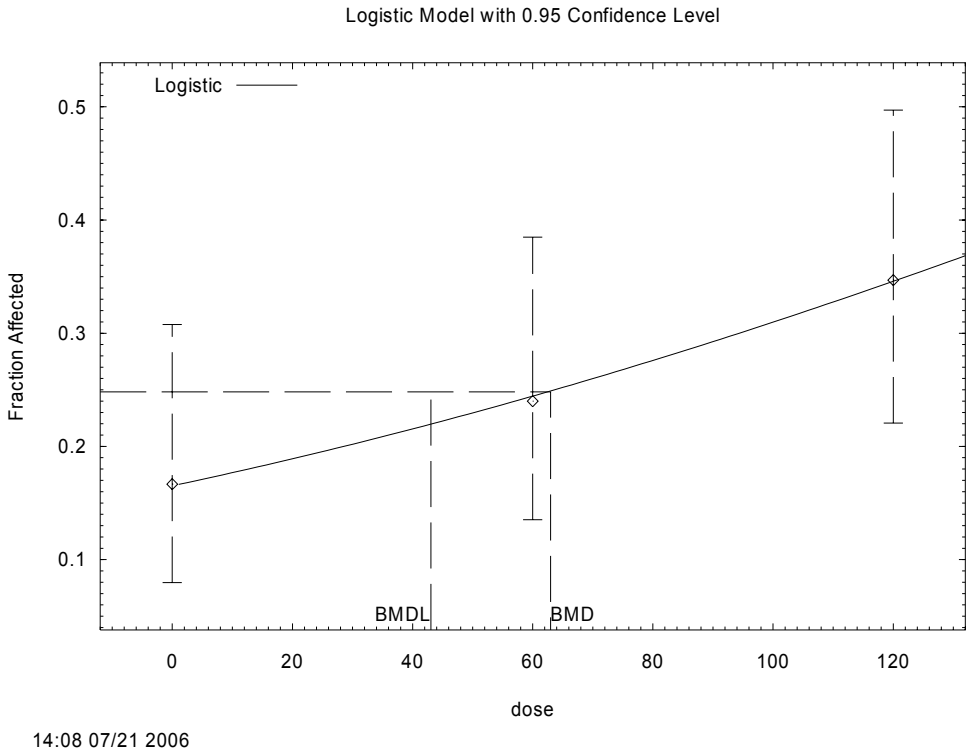
Table A-13. BMD Modeling of Incidence Data for Kidney Lesions in Male Mice Exposed to 1,2-Dichlorobenzene for 103 Weeks

Model	Chi-square p-value	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma[a]	NA	167.62	65.92	29.80
Logistic	0.94	165.63	62.96	43.04
Log-logistic[b]	NA	167.62	65.85	26.33
Multi-stage[c]	0.77	165.71	53.90	29.58
Probit	0.91	165.64	61.60	41.20
Log-probit[b]	0.84	165.67	72.33	46.85
Quantal-linear	0.77	165.71	53.90	29.58
Quantal-quadratic	0.74	165.73	79.20	57.20
Weibull	NA	167.62	66.03	29.80

[a]Restrict power >=1
[b]Slope restricted to >1
[c]Restrict betas >=0; lowest degree polynomial (1-degree) providing adequate fit

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose associated with 10% extra risk; $BMDL_{10}$ = lower confidence limit (95%) on the benchmark dose; NA = Chi-square p-value not applicable (Chi-square = 0; degrees of freedom = 0)

Figure A-5. Observed and Predicted Incidences of Kidney Lesions in Male Mice Exposed to 1,2-Dichlorobenzene for 103 Weeks*



*BMD and BMDL (in mg/kg/day) are associated with a 10% extra risk.

Source: NTP 1985

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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 $BMDL_{10}$ of 43.04 mg/kg/day was duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$BMDL_{10\ ADJ} = (BMDL_{10})\ (\text{days}/7\ \text{days})$$
$$= (43.04\ \text{mg/kg/day})\ (5\ \text{days}/7\ \text{days})$$
$$= 30.74\ \text{mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL: No other studies were located that evaluated effects on renal tissues following chronic oral exposure to 1,2-DCB.

The NOAEL/LOAEL approach to MRL derivation results in a similar chronic-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 60 mg/kg/day for increased incidence of renal tubular regeneration, the NOAEL is duration-adjusted to 43 mg/kg/day (60 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichlorobenzene (1,3-DCB)
CAS Numbers: 541-73-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2
Species: Rat

Minimal Risk Level: [0.4] mg/kg/day [ ] ppm

Reference: McCauley PT, Robinson M, Daniel FB, et al. 1995. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem Toxicol 18(2 & 3):201-221.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,3-DCB in gavage doses of 0, 37, 147, 368, or 735 mg/kg/day in corn oil for 10 consecutive days. End points evaluated during the study included clinical signs, survival, body weight, and food and water consumption. At the end of the study, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), and selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads). Gross pathology was evaluated in all animals, and comprehensive histological examinations were performed in the high dose and control groups; histology in the lower dose groups was limited to the liver. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

Effects noted in study and corresponding doses: No compound-related deaths or overt clinical signs were observed. Body weight was significantly reduced in both sexes at 735 mg/kg/day (20 and 13% lower than controls in males and females, respectively). Food consumption was significantly decreased at 735 mg/kg/day in males (12%, normalized by body weight), and water consumption was significantly increased (8–13%) in females at ≥735 mg/kg/day. The hematological evaluation showed 8% decreased MCV in females at 735 mg/kg/day. The clinical chemistry analyses showed statistically significant changes in several indices, but serum cholesterol was the only end point that had values that exceeded the reference range. Serum cholesterol was significantly increased in females at 368 and 735 mg/kg/day (94 and 63% higher than controls, respectively), as well as in males at 368 and 735 mg/kg/day (79 and 84% higher than controls, respectively). Relative liver weight was significantly increased in males at ≥147 mg/kg/day and females at ≥368 mg/kg/day; increases in the males were 9.1, 31.3, 50.63, and 32.5% higher than controls in the low- to high-dose groups. Other significant changes in relative organ weight included decreased spleen weight in females at ≥368 mg/kg/day and in males at 735 mg/kg/day, decreased thymus weight in both sexes at 735 mg/kg/day, and decreased testes weight in males at 735 mg/kg/day. Absolute organ weights were not reported. Histological changes primarily occurred in the liver, particularly centrilobular hepatocellular degeneration at ≥368 mg/kg/day. This lesion was characterized by varying degrees of cytoplasmic vacuolization and swelling with intact membranes, and occurred in the 368 and 735 mg/kg/day groups in 2/10 and 9/10 males, respectively, and in 6/10 and 10/10 females, respectively; incidences in the other groups were not reported, but are presumed to be 0/10. Other hepatic alterations included hepatocellular necrosis that was sporadically noted in the 147, 368, and 735 mg/kg/day groups. This change was usually minimal to mild, and tended to increase in incidence and severity in the males in a dose-related manner; however, incidences were not reported. The only other reported histological change was atrophy of the thymus, characterized by loss of normal

differentiation between medulla and cortex. The thymic atrophy was observed in 2/10 males (both marked in severity) and 2/9 females (both mild in severity) at 735 mg/kg/day; this change was not observed in controls, and the other dosed groups were not examined. The 147 mg/kg/day dose is a LOAEL based on the >30% increase in relative liver weight in male rats. The NOAEL for increased liver weight is 37 mg/kg/day.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 36.32 mg/kg/day for increased liver weight in female rats is used as the point of departure for the MRL.

BMD analysis was conducted on hepatic effects data in the male and female rats of the McCauley et al. (1995) study. The liver effects data modeled included the incidences of hepatocellular degeneration, absolute liver weights, and mean serum cholesterol levels shown in Table A-14.

Table A-14. Liver Effects Observed in Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Effects	Sex	Dose (mg/kg/day)				
		0	37	147	368	735
Centrilobular hepatocellular degeneration	M	0/10[a]	0/10[a]	0/10[a]	2/10	9/10[b]
	F	0/10[a]	0/10[a]	0/10[a]	6/10[b]	10/10[b]
Absolute liver weight (g)	M	11.04±1.00 n=10	12.06±1.56 n=10	14.5±2.30[b] n=9	16.63±1.62[b] n=10	14.63±2.26[b] n=9
	F	7.68±0.75 n=10	8.12±0.77 n=10	9.18±0.99 n=9	11.90±1.19[b] n=10	12.66±2.55[b] n=9
Mean serum cholesterol (mg/dL)	M	63.0±10.2 n=10	63.6±3.7 n=10	92.4±20.9 n=10	112.5±16.3[b] n=9	116.0±49.6[b] n=10
	F	64.8±12.2 n=8	73.3±10.8 n=10	87.9±13.8 n=9	125.4±27.0[b] n=10	105.7±16.6[b] n=9

[a]Incidences of centrilobular hepatocellular degeneration were not reported for the 0, 37, and 147 mg/kg/day dose groups, but are assumed to be 0/10 each because the lesion was only reported present in the two highest dose groups.
[b]Significantly ($p \leq 0.05$) different from control value.

Source: McCauley et al. 1995

All dichotomous variable models available in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the incidence data for hepatocellular degeneration in male and female rats. A BMR of 10% extra risk was selected in the absence of a biological rationale for selecting an alternative BMR. The modeling results are shown in Table A-15. All dichotomous models provided adequate fit to the male and female hepatocellular degeneration incidence data, as determined by Chi-square p-values >0.1 (Table A-15). The log-probit model was determined to be the best-fitting (lowest AIC) model for the male data and provided a BMD_{10} of 319.18 mg/kg/day and a $BMDL_{10}$ of 207.86 mg/kg/day. The log-logistic model was determined to be the best-fitting (lowest AIC) model for the female data and provided a BMD_{10} of 318.46 mg/kg/day and a $BMDL_{10}$ of 159.37 mg/kg/day.

Table A-15. Modeling Results for Incidences of Centrilobular Degeneration in Male and Female Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Males				
Gamma[b]	0.9997	20.53	314.37	196.42
Logistic	0.9386	21.15	322.99	215.61
Log-logistic[c]	0.9992	20.55	317.16	206.86
Multi-stage[d]	0.9895	20.72	305.72	156.48
Probit	0.9787	20.81	316.14	205.06
Log-probit[c]	1.0000	20.51	319.18	207.86
Quantal linear	0.1153	28.95	82.93	51.49
Quantal quadratic	0.7150	21.46	190.83	148.00
Weibull[b]	0.9918	20.69	306.04	182.80
Females				
Gamma[b]	1.00	15.48	251.73	145.75
Logistic	1.00	17.46	338.16	167.41
Log-logistic[c]	1.00	15.46	318.46	159.37
Multi-stage[d]	0.97	15.92	216.50	124.71
Probit	1.00	17.46	310.54	153.36
Log-probit[c]	1.00	17.46	303.18	153.81
Quantal linear	0.13	28.04	45.74	29.88
Quantal quadratic	0.75	19.06	128.58	99.32
Weibull[b]	1.00	17.46	313.61	138.53

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

AIC = Akaike's Information Criteria; BMD_{10} = benchmark dose associated with a 10% extra risk; $BMDL_{10}$ = lower confidence limit (95%) on the benchmark dose

All continuous variable models in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the mean absolute liver weight data and mean serum cholesterol level data from the male and female rats. A BMR of 1 standard deviation increase above the control mean was selected in the absence of a biological rationale for using an alternative BMR. None of the available models provided adequate mean fit to the male rat absolute liver weight data or the female rat serum cholesterol data, based on p-values <0.01 for mean fit. Modeling of the male rat serum cholesterol data resulted in failed tests for both constant and non-homogeneous variance.

For the female rat absolute liver weight data, results of testing for constant and non-homogeneous variance indicated that a non-homogeneous variance assumption was appropriate. The modeling results are shown in Table A-16. Based on this assumption, the linear, 2-degree polynomial, and Hill models provided adequate mean fit to the female rat absolute liver weight data. The power model provided a p-value of 0.093, which was considered adequate, although a p-value >0.1 is the conventional goodness-

of-fit standard. Although the Hill model provided adequate mean fit, it failed to determine a BMDL and was rejected from further consideration for selection of a point of departure for deriving an acute-duration oral MRL. The best-fitting model for the female rat absolute liver weight data was the 2-degree polynomial model (lowest AIC), which provided a BMD_{1sd} of 51.83 mg/kg/day and a $BMDL_{1sd}$ of 36.32 mg/kg/day.

In summary, BMD analysis of liver effects in the male and female rats of the principal study (McCauley et al. 1995) resulted in a $BMDL_{10}$ of 207.86 mg/kg/day for hepatocellular degeneration in male rats (best-fitting [log-probit] model), a $BMDL_{10}$ of 159.37 mg/kg/day for hepatocellular degeneration in female rats (best-fitting [log-probit] model), and a $BMDL_{1sd}$ of 36.32 mg/kg/day for absolute liver weight changes in female rats (best-fitting [2-degree polynomial] model). Using a conservative approach, the $BMDL_{1sd}$ of 36.32 mg/kg/day for absolute liver weight changes in female rats (Table A-16, Figure A-6) is selected as the point of departure for deriving an MRL. The $BMDL_{1sd}$ of 36.32 mg/kg/day was divided by an uncertainty factor of 100 to derive an MRL of 0.4 mg/kg/day.

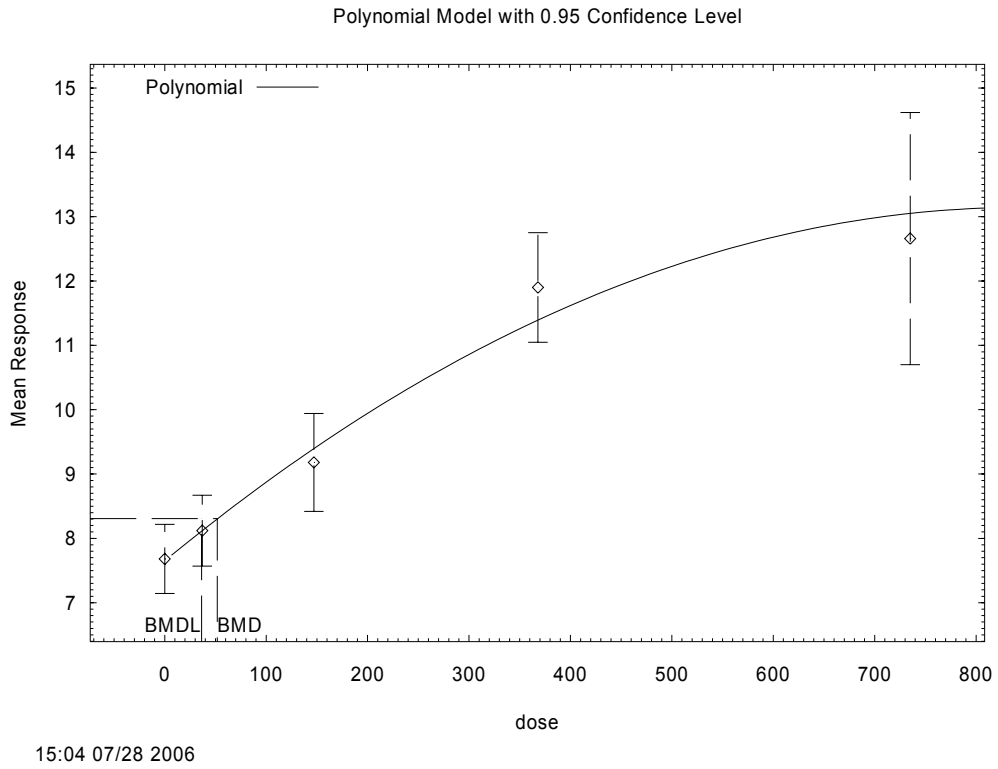
Table A-16. Modeling Results for Absolute Liver Weight Data in Female Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Linear[b,c]	0.0002	NA	NA	NA	NA
Linear[c,d]	0.36	0.15	68.39	76.09	55.09
Polynomial[c,e]	0.36	0.62	66.046	51.83	36.32
Power[d,f]	0.29	0.093	70.39	76.08	55.09
Hill[d,g]	0.36	0.37	67.87	78.40	No value

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Non-homogeneous variance assumed
[e]Lowest degree polynomial (2-degree) providing adequate fit
[f]Restrict power >=1
[g]Restrict n>1

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose associated with one standard deviation increase above control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; F= BMDL computation failed due to bad completion code in Optimization routine; NA = not applicable, as model does not provide adequate fit

Figure A-6. Observed and Predicted Liver Weights in Female Rats Exposed to 1,3-Dichlorobenzene for 10 Days*



*BMD and BMDL (in mg/kg/day) are for a 1 standard deviation increase above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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

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

Other additional studies or pertinent information that lend support to this MRL: No additional acute-duration studies of 1,3-DCB were located.

The NOAEL/LOAEL approach to MRL derivation results in same MRL as the 0.4 mg/kg/day value derived using the benchmark dose approach. Using the 37 mg/kg/day NOAEL for increased liver weight and the uncertainty factor of 100, the NOAEL/LOAEL approach yields an MRL of 0.4 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichlorobenzene (1,3-DCB)
CAS Numbers: 541-73-1
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: [0.02] mg/kg/day [ ] ppm

Reference: McCauley PT, Robinson M, Daniel FB, et al. 1995. Toxicity studies of 1,3-dichlorobenzene in Sprague-Dawley rats. Drug Chem Toxicol 18(2 & 3):201-221.

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were administered 1,3-DCB in gavage doses of 0, 9, 37, 147, or 588 mg/kg/day in corn oil for 90 consecutive days (McCauley et al. 1995). End points evaluated during the study included clinical signs and mortality, body weight, and food and water consumption. At end of the exposure period, blood was collected for hematology and serum chemistry analyses (erythrocytes, leukocytes, hemoglobin, hematocrit, mean corpuscular volume, glucose, BUN, creatinine, AP, AST, ALT, cholesterol, LDH, and calcium levels), selected organs were weighed (brain, liver, spleen, lungs with lower half of trachea, thymus, kidneys, adrenal glands, heart, and gonads), and gross pathology was assessed. Histological examinations were performed on all tissues that were examined grossly in all high-dose rats and in one-half of control rats, as well as in the liver, thyroid, and pituitary glands from all animals in the 9, 37, and 147 mg/kg/day dose groups. Inflammatory and degenerative lesions were graded on a relative scale from one to four depending on the severity (minimal, mild, moderate, or marked).

Effects noted in study and corresponding doses: No compound-related deaths or overt clinical signs were observed. Body weight was reduced in both sexes at 588 mg/kg/day (24 and 10% lower than controls in males and females, respectively). The decreased weight gain was progressive throughout the exposure period and occurred despite increased food and water consumption in the same groups. Other effects included increased relative kidney weight in males at ≥147 mg/kg/day and in females at 588 mg/kg/day, but there were no renal histopathological changes in any of the exposed animals. Hematological alterations consisted of significant increases in leukocyte levels in males at 147 mg/kg/day and in females at 588 mg/kg/day, and erythrocyte levels in males at 588 mg/kg/day. Histopathology and serum chemistry findings indicated that the thyroid, pituitary, and liver were the most sensitive targets of toxicity, as discussed below. The lowest LOAEL is 9 mg/kg/day, which is the lowest tested dose and a minimal LOAEL for thyroid and liver effects.

Thyroid effects included significantly ($p \leq 0.05$) increased incidences of reduced colloidal density in follicles that exceeded normal variability in male rats at ≥9 mg/kg/day and in female rats at ≥37 mg/kg/day (control to high dose group incidences of 2/10, 8/10, 10/10, 8/9, and 8/8 in males, and 1/10, 5/10, 8/10, 8/10, and 8/9 in females). Depletion of colloid density in the thyroid was characterized by decreased follicular size with scant colloid and follicles lined by cells that were cuboidal to columnar. The severity of the colloid density depletion generally ranged from mild to moderate, increased with dose level, and was greater in males than females. Incidences of male rats with thyroid colloidal density depletion of moderate or marked severity were significantly increased at ≥147 mg/kg/day (0/10, 0/10, 2/10, 5/9, and 6/8). The 9 mg/kg/day dose is considered to be a minimal LOAEL for thyroid effects

because the morphological alterations (reduced colloidal density in follicles) are unlikely to be associated with functional changes in the thyroid.

Pituitary effects included significantly ($p \leq 0.05$) increased incidences of cytoplasmic vacuolization in the pars distalis in male rats at ≥147 mg/kg/day (2/10, 6/10, 6/10, 10/10, 7/7). The vacuoles were variably sized, irregularly shaped, and often poorly defined, and the severity of the lesions (i.e., number of cells containing vacuoles) ranged from minimal to mild and generally increased with increasing dose level. Incidences of male rats with pituitary cytoplasmic vacuolization of moderate or marked severity were significantly increased at 588 mg/kg/day (1/10, 0/10, 2/10, 3/9, and 7/7). The pituitary lesion was reported to be similar to "castration cells" found in gonadectomized rats and considered to be an indicator of gonadal deficiency. No compound-related pituitary lesions were observed in female rats. Serum cholesterol was significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day in a dose-related manner, and serum calcium was significantly increased in both sexes at ≥37 mg/kg/day. The investigators suggested that these serum chemistry changes might reflect a disruption of hormonal feedback mechanisms, or target organ effects on the pituitary, hypothalamus, and/or other endocrine organs. Based on the increased incidences of cytoplasmic vacuolation, the LOAEL for pituitary effects is 147 mg/kg/day.

Hepatic effects occurred in both sexes at 147 and 588 mg/kg/day, including significantly increased relative liver weight and incidences of liver lesions. Absolute organ weights were not reported. Liver lesions were characterized by inflammation, hepatocellular alterations (eosinophilic homogeneous inclusions), and hepatocellular necrosis. Liver lesions that were significantly ($p \leq 0.05$) increased included hepatocellular cytoplasmic alterations of minimal to mild severity in males at ≥147 mg/kg/day (1/10, 2/10, 1/10, 6/10, 7/9) and in females at 588 mg/kg/day (0/10, 2/10, 0/10, 1/10, 7/9), and necrotic hepatocyte foci of minimal severity at 588 mg/kg/day in both males (1/10, 2/10, 1/10, 2/10, 5/9) and females (0/10, 0/10, 0/10, 3/10, 5/9). Other statistically significant liver-associated effects included significantly increased serum AST levels (90–100% higher than controls) in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day. Serum cholesterol levels were significantly increased in males at ≥9 mg/kg/day and in females at ≥37 mg/kg/day, but might be pituitary-related, as indicated above. Serum LDH levels were reduced in males at ≥9 mg/kg/day and BUN levels were reduced in both sexes at 588 mg/kg/day, but the biological significance of decreases in these indices is unclear. The 9 mg/kg/day dose is considered to be a minimal LOAEL for liver effects because the main effect, increased serum AST, showed no clear dose-response and was only accompanied by necrotic liver lesions at a much higher dose (588 mg/kg/day).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{10}$ of 2.1 mg/kg/day for increased incidences of pituitary lesions is used as the basis for the MRL.

Benchmark dose analysis was conducted using the thyroid and pituitary lesion incidence data and serum AST and cholesterol levels summarized in Table A-17.

Table A-17. Thyroid, Pituitary and Liver Effects in Rats Orally Exposed to 1,3-Dichlorobenzene for 90 Days

Effect	Sex	Dose (mg/kg/day)				
		0	9	37	147	588
Thyroid, reduced follicular colloidal density	M	2/10	8/10[a]	10/10[a]	8/9[a]	8/8[a]
Pituitary, cytoplasmic vacuolation in pars distalis	M	2/10	6/10	6/10	10/10[a]	7/7[a]
Serum AST (U/L) (mean ± SD)	M	43.7 ± 37.7 (n=10)	87.6 ± 24.7[a] (n=10)	109.8 ± 9.5 (n=10)	88.0 ± 23.3[a] (n=10)	82.8 ± 13.8[a] (n=8)
Serum cholesterol (mg/dL) (mean ± SD)	M	73.5 ± 1.4 (n=10)	96.6 ± 1.7[a] (n=10)	111.1 ± 1.6[a] (n=10)	157.9 ± 2.5[a] (n=10)	89.5 ± 1.5[a] (n=8)
Serum cholesterol (mg/dL) (mean ± SD)	F	68.2 ± 1.7 (n=10)	85.0 ± 3.0 (n=10)	108.4 ± 2.2[a] (n=10)	158.9 ± 1.8[a] (n=10)	152.6 ± 2.6[a] (n=9)

[a]Significantly ($p \leq 0.05$) different from control

Source: McCauley et al. 1995

Continuous variable models (linear, polynomial, power, and Hill) in the EPA Benchmark Dose Software (Version 1.3.2) were fit to the serum AST levels in the male rats and the serum cholesterol levels in the male and female rats. One standard deviation change from the control mean was selected as the BMR for each data set in the absence of a biological rationale for an alternative BMR. Initial modeling results using constant variance indicated that modeling should be performed using non-homogeneous variance. However, modeling results using non-homogeneous variance for each of the continuous variable models resulted in inadequate mean fit to the serum AST and cholesterol data, as indicated by p-values <0.0001 for mean fit.

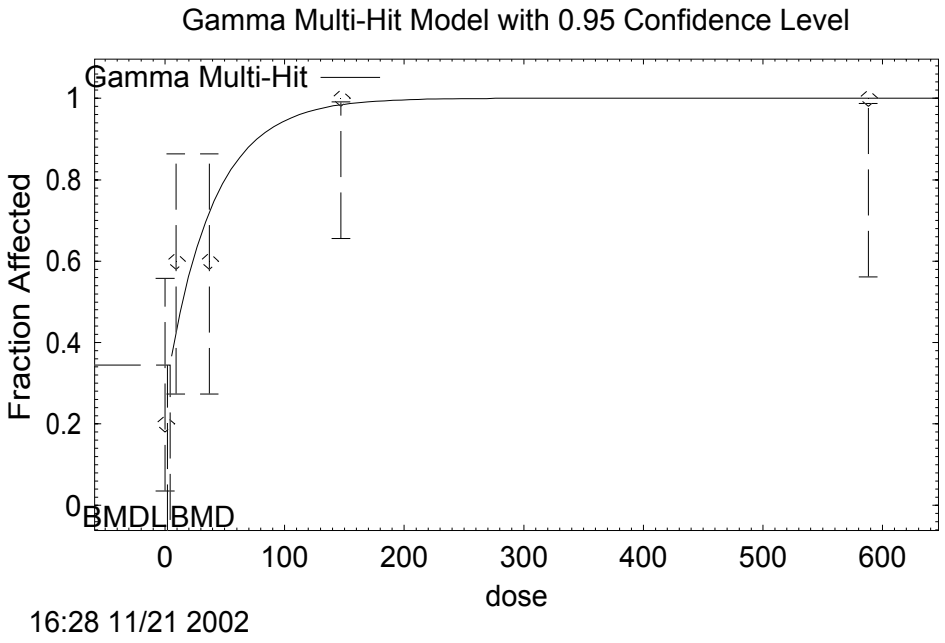
Dichotomous variable models available in the EPA Benchmark Dose Software were fit to the male rat incidence data for: (1) reduced follicular colloidal density in the thyroid, and (2) cytoplasmic vacuolation in the pars distalis of the pituitary. For each variable, AIC was used to select the best-fitting model from which BMDs and BMDLs were calculated, using a BMR of 10% extra risk. For the thyroid incidence data, none of the available dichotomous variable models provided adequate fit as indicated by chi-square goodness of fit p-values ≤0.002. For the pituitary cytoplasmic vacuolation incidence data, all of the models provided adequate fit as indicated by chi-square goodness of fit p-values >0.1 (Table A-18). The probit model provided the lowest AIC (43.442). However, a nearly identical AIC value (43.467) was provided by each of three other models (gamma, quantal-linear, and Weibull). Because the BMD_{10} of 4.08 mg/kg/day and associated $BMDL_{10}$ of 2.10 mg/kg/day from the gamma, quantal-linear, and Weibull models are lower than those from the probit model (BMD_{10} = 7.79 mg/kg/day; $BMDL_{10}$ = 4.46 mg/kg/day), a conservative health protective approach was taken and the lower $BMDL_{10}$ of 2.10 mg/kg/day was selected as the point of departure for deriving the MRL (Table A-18, Figure A-7). The $BMDL_{10}$ of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) to derive an MRL of 0.02 mg/kg/day.

Table A-18. BMD Modeling Results of Incidence Data for Pituitary Lesions in Male Rats Exposed to 1,3-Dichlorobenzene for 90 Days

Model	Chi-square p-value[a]	AIC	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Probit	0.4823	43.442	7.79	4.46
Gamma[b]	0.4887	43.467	4.08	2.1
Quantal-linear	0.4887	43.467	4.08	2.1
Weibull[b]	0.4887	43.467	4.08	2.1
Logistic	0.4639	43.58	7.49	4.29
Quantal-quadratic	0.376	44.122	17.11	10.10
Log-probit[c]	0.3154	44.674	7.33	3.29
Multi-stage[d]	0.3061	45.350	5.21	2.28
Log-logistic[c]	0.2190	46.518	2.34	0.66

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Restrict power >=1
[c]Slope restricted to >1
[d]Restrict betas ≥0; Degree of polynomial=2

Figure A-7. Observed Incidences for Pituitary Lesions in Male Rats and Incidences Predicted by the Gamma Model*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 10% extra risk. The gamma model plot in this figure is identical to plots produced by the quantal-linear and Weibull models.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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

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

Other additional studies or pertinent information that lend support to this MRL: No additional intermediate-duration studies of 1,3-DCB were located.

The NOAEL/LOAEL approach to MRL derivation provides support to the MRL of 0.02 mg/kg/day based on the BMD analysis of pituitary lesions. The lowest tested dose of 9 mg/kg/day is considered a minimal LOAEL for thyroid lesions and increases in serum AST. Using the minimal LOAEL of 9 mg/kg/day and an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), the NOAEL/LOAEL approach yields an MRL of 0.03 mg/kg/day.

Agency Contact (Chemical Manager): Malcolm Williams, DVM, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 44
Species: Dog

Minimal Risk Level: [0.07] mg/kg/day [ ] ppm

References: Naylor MW, Stout LD. 1996. One year study of p-dichlorobenzene administered orally via capsule to beagle dogs. Environmental Health Laboratory, Monsanto Company, St. Louis, MO. Study No. ML-94-210, March 25, 1996. MRID# 43988802. Unpublished.

EPA. 1996b. Data Evaluation Record (DER) for p-dichlorobenzene – chronic oral toxicity in dogs (MRID# 439888-01 and -02) for Section 6 (a) (2) and reregistration need. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.

Experimental design: Groups of five male and five female beagle dogs were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day for 1 year. Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average level reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high dose males and females were untreated during weeks 4 and 5 to allow for recovery. End points evaluated throughout the study included clinical observations (daily), body weight (weekly), and food consumption (weekly). Ophthalmoscopic examinations were performed prior to study start and just prior to study completion. Hematology (11 indices, including activated partial thromboplastin time), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase), and urinalysis (10 indices) were performed at month 6 and study completion. Organ weights, gross pathology, and histology were evaluated at study completion.

Effects noted in study and corresponding doses: Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed in extremis on day 12, one male death on day 25, and one female death on day 24. A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred after 6 and 12 months at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and/or histopathology. Effects on serum enzyme levels included significantly increased AP in males at 50 mg/kg/day at months 6 and 12 (731 and 620% higher than controls, respectively), females at 50 mg/kg/day at months 6 and

12 (525 and 330% higher), and females at 75 mg/kg/day at months 6 and 12 months (761 and 680% higher). Serum AP levels were not statistically significantly increased in the 75 mg/kg/day males at months 6 or 12, but only 3 animals were evaluated in this dose group. Other clinical chemistry findings included significantly increased ALT in females at 75 mg/kg/day at month 12 (253% higher than controls), increased GGTP in females at 75 mg/kg/day at months 6 and 12 (131 and 161% higher), and decreased albumin in males at 50 and 75 mg/kg/day at month 6 (16 and 18% lower than controls) and females at 75 mg/kg/day at month 6 (19% lower). Absolute and relative liver weights were significantly increased (40–70% higher than controls) in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatic lesions included hepatocellular hypertrophy (diffuse or multifocal in all males and females at 50 and 75 mg/kg/day and one female at 10 mg/kg/day), hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day.

The highest NOAEL and lowest LOAEL are 10 and 50 mg/kg/day, respectively, based on the increases in serum AP at 6 months. This serum enzyme change is a sufficient indication of intermediate-duration hepatotoxicity because the increases were similar in magnitude to those that were observed after 1 year and associated with increased liver weight and liver lesions; the latter effects likely developed earlier in the study but could not be detected due to the lack of organ weight and histology examinations at 6 months.

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 10 mg/kg/day for increased serum AP is used as the basis for the MRL.

BMD analysis was conducted using the Naylor and Stout (1996) data for changes in serum AP in female dogs administered 1,4-DCB orally for 6 months, as shown in Table A-19. A BMR of 1 standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. Mean serum AP levels in the female dogs exhibited a dose-response relationship and were significantly higher in the 50 and 75 mg/kg/day groups, relative to controls. Although significantly increased mean serum AP levels were noted in the 50 mg/kg/day male dogs, the increase was not significant in the 75 mg/kg/day males; only three males in this dose group were available for the assessment of serum AP levels. Therefore, the male serum AP data were not modeled. The simplest model (linear) for continuous data from the EPA Benchmark Dose Software (Version 1.3.2) was initially fit to the female serum AP data; constant variance was selected. As shown in Table A-20, the linear model output indicated inadequate fit for constant variance (as indicated by a p-value <0.01 for the test of constant variance) and a model run using nonhomogeneous variance was suggested. However, using nonhomogeneous variance, inadequate model mean fit was obtained (p-value <0.01 for model mean fit) (see Table A-20). The more complex (polynomial, power, Hill) models were also fit to the serum AP data. The Hill model provided inadequate mean fit due to an insufficient number of dose groups (4, including controls), which resulted in insufficient (0) degrees of freedom. Both the polynomial and power models provided adequate mean fit (Table A-20). Following conventional protocol for selection of the point of departure (the adequate model with the lowest AIC [Akaike's Information Criteria]), the

$BMDL_{1sd}$ of 9.97 mg/kg/day (lower 95% confidence limit on the BMD_{1sd} of 12.48 mg/kg/day) was selected as the point of departure for deriving an intermediate-duration oral MRL for 1,4-DCB (see Table A-20, Figure A-8). The $BMDL_{1sd}$ of 9.97 mg/kg/day was duration-adjusted to 7 mg/kg/day and divided by an uncertainty factor of 100 to derive an MRL of 0.07 mg/kg/day.

Table A-19. Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months

Dose (mg/kg/day)	Group size	Mean serum AP level in IU/L (percent of control mean)
0	5	175.80 ± 50.05[a] --
10	5	176.00 ± 64.50 (100)
50	5	1098.20[b] ± 425.85 (625)
75	4	1513.50[c] ± 855.31 (861)

[a]Standard deviation
[b]Significantly different (p<0.01) from control group
[c]Significantly different (p<0.05) from control group

Source: Naylor and Stout 1996

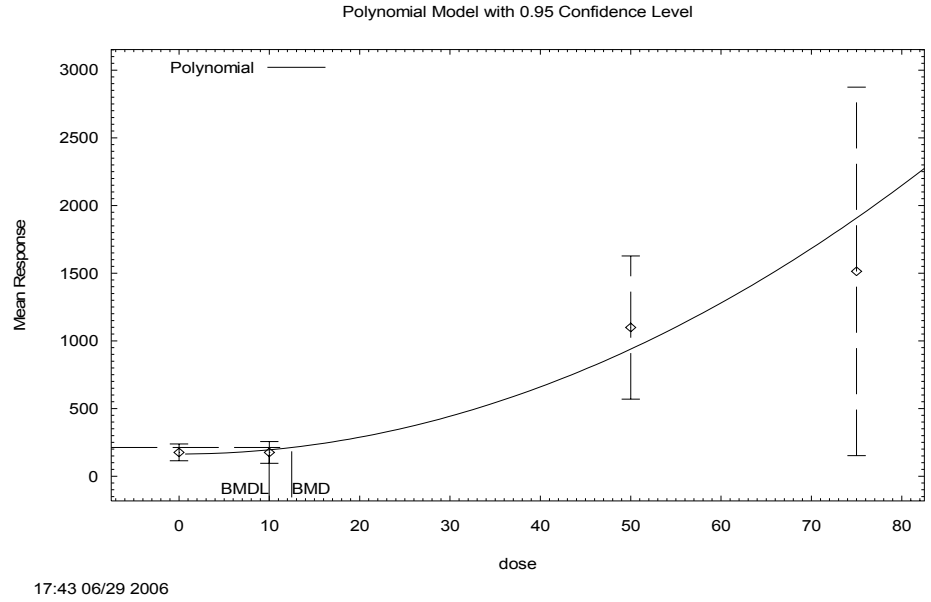
Table A-20. Model Predictions for Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{1sd} (mg/kg/day)	$BMDL_{1sd}$ (mg/kg/day)
Linear[b,c]	<0.01	NA	NA	NA	NA
Linear[c,d]	NA	<0.01	NA	NA	NA
2-Degree polynomial[c,d]	**0.776**	**0.13**	**220.61**	**12.48**	**9.97**
Power[d]	0.774	0.14	222.59	12.00	6.62

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonhomogeneous variance assumed

BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation above the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; NA = not applicable because model failed a goodness-of-fit test

Figure A-8. Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 6 Months*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 1 standard deviation above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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 $BMDL_{1sd}$ of 10 mg/kg/day was adjusted to a continuous exposure scenario as follows:

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (5days/7\ days)$$
$$= (10\ mg/kg/day)\ (5\ days/7\ days)$$
$$= 7\ mg/kg/day$$

Other additional studies or pertinent information that lend support to this MRL: The NOAEL/LOAEL approach to MRL derivation results in the same intermediate-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 10 mg/kg/day for increased serum AP in dogs (Naylor and Stout 1996), the NOAEL is duration-adjusted to 7 mg/kg/day (10 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.07 mg/kg/day.

Information on the systemic toxicity of intermediate-duration oral exposure to 1,4-DCB is available from a number of studies conducted in rodents, mainly rats and mice, as well as the MRL study in dogs. Liver

and kidney effects are the most consistently observed, best characterized, and most sensitive findings in these studies. The lowest observed adverse effect level is for liver toxicity in dogs, although reproductive and developmental studies in rats indicate that offspring are particularly sensitive to 1,4-DCB toxicity during the postnatal pre-weaning period.

Hepatic effects induced by intermediate-duration oral exposures to 1,4-DCB ranged from increased liver weight and hepatocyte enlargement to hepatocellular degeneration, lesions, necrosis, and tumors in rats, mice, rabbits, and dogs. Increases in serum levels of enzymes and alterations in other end points (e.g., serum cholesterol and triglycerides) indicative of hepatocellular damage or liver dysfunction have also been induced. Increased liver weight is the most sensitive hepatic end point in subchronic studies in rats, observed at doses as low as 150 mg/kg/day for 4–13 weeks and 188 mg/kg/day for 192 days (Hollingsworth et al. 1956; Lake et al. 1997; Umemura et al. 1998). There was no indication of early liver damage in rats exposed to 150 mg/kg/day for 4 weeks using an immunohistochemical marker of centrilobular hepatocyte injury (Umemura et al. 1998), and increases in liver porphyrins in rats exposed to 50–200 mg/kg/day for 120 days were not considered to be toxicologically significant (Carlson 1977). Hepatocellular hypertrophy and decreased serum triglycerides occurred in rats exposed to ≥300 mg/kg/day for 13 weeks (NTP 1987; Lake et al. 1997). Higher dose levels of 1,4-DCB induced degenerative liver lesions in rats exposed to 376 mg/kg/day for 192 days (slight cirrhosis and focal necrosis) (Hollingsworth et al. 1956) or 1,200 mg/kg/day for 13 weeks (hepatocyte degeneration and necrosis) (NTP 1987). In mice, hepatocellular degeneration was induced at doses ≥600 mg/kg/day for 13 weeks (NTP 1987), and rabbits had cloudy swelling and minimal focal necrosis in the liver after exposure to 500 mg/kg/day for 367 days (Hollingsworth et al. 1956). Dogs are more sensitive to hepatic effects of 1,4-DCB than the other species based on increases in serum enzymes following exposure to doses as low as 50 mg/kg/day for 6 months in the MRL study (Naylor and Stout 1996).

Kidney effects, including collecting duct epithelial vacuolation, are additional effects of 1,4-DCB in the dogs exposed to ≥50 mg/kg/day for 1 year in the MRL study (Naylor and Stout 1996). Renal changes, including hyaline droplet accumulation, increased kidney weights, and tubular lesions, are characteristically observed effects of subchronic and chronic oral exposure to 1,4-DCB in male rats at doses ≥75 mg/kg/day (Bomhard et al. 1988; Lake et al. 1997; NTP 1987). These findings were not considered for MRL derivation because there is a scientific consensus that they are related to the α2μ-globulin nephropathy syndrome, which is specific to male rats and not relevant to humans. Subchronic studies in female rats found increased kidney weight, but no indications of nephrotoxic action (i.e., no histopathology or effects on urinary indices of renal function), following exposure to ≥188 mg/kg/day for 192 days or 600 mg/kg/day for 13 weeks (Bomhard et al. 1988; Hollingsworth et al. 1956).

Developmental toxicity studies provide no indications that 1,4-DCB is teratogenic in rats at oral doses as high as 1,000 mg/kg/day during gestation, although fetotoxicity occurred at maternally toxic levels ≥500 mg/kg/day (Giavini et al. 1986; Ruddick et al. 1983). Decreased maternal weight gain and increased incidences of extra ribs, a skeletal variation attributable to the maternal toxicity, occurred in rats at gestational dose levels ≥500 mg/kg/day, but not at 250 mg/kg/day (Giavini et al. 1986). In a 2-generation study, reproductive and developmental toxicity were evaluated in male and female rats that were orally exposed to 30, 90, or 270 mg/kg/day of 1,4-DCB (Bornatowicz et al. 1994). No effects on mating and fertility indices were observed at any level, although toxicity occurred in the offspring at doses ≥90 mg/kg/day. Effects at ≥90 mg/kg/day included reduced birth weight in F_1 pups and increased total number of deaths from birth to postnatal day 4 in F_1 and F_2 pups, clinical manifestations of dry and scaly skin (until approximately postnatal day 7) and tail constriction with occasional partial tail loss (during postnatal days 4–21) in F_1 and F_2 pups, reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F_2 pups, and increased relative liver weight in adult F_1 males. No exposure-

related changes were found at 30 mg/kg/day, indicating that this is the NOAEL for reproductive and developmental toxicity in rats.

As indicated above, liver, kidney, and perinatal developmental toxicity are main effects of concern for intermediate-duration oral exposure to 1,4-DCB in animals. The dog is the most sensitive tested species, as liver effects were induced by exposure to doses as low as 50 mg/kg/day for 6 months (Naylor and Stout 1996), which are below subchronic LOAELs of approximately 150–200 mg/kg/day for liver and kidney effects in rats and mice. The two-generation study in rats demonstrates that oral exposure to 1,4-DCB can cause perinatal developmental toxicity, including reduced birth weight and neonatal survival in F_1 and F_2 pups, at doses $\geq$90 mg/kg/day (Bornatowicz et al. 1994). Although this finding indicates that perinatal developmental toxicity is an additional sensitive end point for 1,4-DCB exposure, the hepatotoxicity induced in dogs at the 50 mg/kg/day dose level (Naylor and Stout 1996) is a more appropriate basis for MRL derivation.

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dichlorobenzene (1,4-DCB)
CAS Numbers: 106-46-7
Date: August 2006
Profile Status: Post-Public, Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61
Species: Dog

Minimal Risk Level: [0.07] mg/kg/day [ ] ppm

References: Naylor MW, Stout LD. 1996. One year study of p-dichlorobenzene administered orally via capsule to beagle dogs. Environmental Health Laboratory, Monsanto Company, St. Louis, MO. Study No. ML-94-210, March 25, 1996. MRID# 43988802. Unpublished.

EPA. 1996b. Data Evaluation Record (DER) for p-dichlorobenzene – chronic oral toxicity in dogs (MRID# 439888-01 and -02) for Section 6 (a) (2) and reregistration need. U.S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances.

Experimental design: Groups of five male and five female beagle dogs were orally administered 1,4-DCB by capsule in dose levels of 0, 10, 50, or 75 mg/kg/day for 1 year. Based on the summarized design of a 4-week dose range-finding study, it is presumed that dosing was 5 days/week. The 75 mg/kg/day dose is a time-weighted average level reflecting dose decreases at the beginning of the study in response to unexpected severe toxicity. An initial high dose of 150 mg/kg/day was adjusted to 100 mg/kg/day for males during week 3, and a further decrease to 75 mg/kg/day was made for both sexes at the beginning of week 6. Both high-dose males and females were untreated during weeks 4 and 5 to allow for recovery. End points evaluated throughout the study included clinical observations (daily), body weight (weekly), and food consumption (weekly). Ophthalmoscopic examinations were performed prior to study start and just prior to study completion. Hematology (11 indices, including activated partial thromboplastin time), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase), and urinalysis (10 indices) were performed at month 6 and study completion (month 12). Organ weights, gross pathology, and histology were evaluated at month 12.

Effects noted in study and corresponding doses: Mortality occurred the first 25 days of the study before dose reduction; exposure to 150 mg/kg/day caused one male dog to be sacrificed in extremis on day 12, one male death on day 25, and one female death on day 24. A control male died on day 83, but all other dogs survived to the end of the study. Treatment-related clinical signs were primarily limited to severely affected high-dose dogs and the control male that died; these included hypoactivity, dehydration, decreased defecation, blood-like fecal color, emesis, emaciation, and/or pale oral mucosa. There were no significant group differences in mean body weight at the end of the study. Body weight gain was significantly reduced during the first month of the study, but recovered following dose reduction and adjustment of food availability. A mild anemia was observed at month 6 (significantly reduced red blood cells in females and HCT in males) at 75 mg/kg/day, but resolved by the end of the study. The mild anemia correlated with histologic findings of bone marrow erythroid hyperplasia in females, and splenic excessive hematopoiesis and megakaryocyte proliferation in both sexes, indicating a compensatory response to the earlier anemia. Hepatic effects occurred at ≥50 mg/kg/day in both sexes as shown by changes in liver enzymes, increased liver weight, and histopathology. Effects on serum enzyme levels included significantly increased AP in males at 50 mg/kg/day at months 6 and 12 (731 and 620% higher than controls, respectively), females at 50 mg/kg/day at months 6 and 12 (525 and 330% higher), and

females at 75 mg/kg/day at months 6 and 12 months (761 and 680% higher). Serum AP was also increased in males at 75 mg/kg/day after 6 and 12 months, but the changes were not statistically significant, possibly due to a reduced group size of 3 males at 75 mg/kg/day. Other clinical chemistry findings included significantly increased ALT in females at 75 mg/kg/day at month 12 (253% higher than controls), increased GGTP in females at 75 mg/kg/day at months 6 and 12 (131 and 161% higher), and decreased albumin in males at 50 and 75 mg/kg/day at month 6 (16 and 18% lower than controls) and females at 75 mg/kg/day at month 6 (19% lower). Absolute and relative liver weights were significantly increased (40-70% higher than controls) in both sexes at 50 and 75 mg/kg/day (except absolute liver weight in 50 mg/kg/day males). Hepatocellular hypertrophy (diffuse or multifocal) occurred in all males and females at 50 and 75 mg/kg/day and in one female at 10 mg/kg/day. The study authors (Naylor and Stout 1996) considered the hepatocellular hypertrophy (multifocal) in the single 10 mg/kg/day female dog to be an adaptive response to a xenobiotic agent rather than a direct treatment-related effect. Other liver lesions considered to be treatment-related included hepatocellular pigment deposition (two males and one female each at 50 and 75 mg/kg/day), bile duct/ductule hyperplasia (one male and one female at 75 mg/kg/day), and hepatic portal inflammation (periportal accumulation of neutrophils in one male at 50 mg/kg/day and two males at 75 mg/kg/day). Kidney effects included collecting duct epithelial vacuolation in one male at 75 mg/kg/day and at all dose levels in females (one each at 10 and 50 mg/kg/day and two at 75 mg/kg/day). The renal lesion was considered to be a possible effect of treatment at ≥50 mg/kg/day, because it was accompanied by increased relative kidney weight in females at ≥50 mg/kg/day and grossly observed renal discoloration in two females at 75 mg/kg/day. The highest NOAEL and lowest LOAEL are 10 and 50 mg/kg/day, respectively, based on the hepatic effects (increased liver weight, changes in liver enzymes, and histopathology).

Dose and end point used for MRL derivation:

[ ] NOAEL [ ] LOAEL [X] BMDL

As discussed below, a $BMDL_{1sd}$ of 10 mg/kg/day for increased serum AP is used as the basis for the MRL.

BMD analysis was performed on serum AP level and relative liver weight data for the female dogs exposed to 1,4-DCB for 1 year. The incidences of hepatocellular hypertrophy in the females (0/5, 1/5, 5/5, and 5/5 at 0, 10, 50, and 75 mg/kg/day) and males (0/5, 0/5, 5/5, and 5/5) are inappropriate for BMD modeling due to actual or effective responses of 0% in the control and low dose groups and 100% in the higher dose groups. The response in the low-dose female dog is effectively 0% because the authors implied that the hypertrophy in this single animal was not a hepatotoxic response. The incidences of the other liver lesions were not subjected to BMD analysis due to the low numbers of responders and group sizes. The data that were modeled are shown in Table A-21; the modeling results are shown in Table A-22.

Table A-21. Selected Liver Effects in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months

Dose (mg/kg/day)	Group size	Mean serum AP in IU/L (percent of control mean)	Mean relative liver weight in percent (percent of control mean)
0	5	173.40±55.09[a] --	2.71±0.17[a] --
10	5	181.80±69.22 (105)	3.05±0.83 (113)
50	5	745.80[c]±329.53 (430)	4.20[c]±0.47 (155)
75	4	1351.75[b]±652.46 (780)	4.61[c]±0.70 (170)

[a]Standard deviation
[b]Significantly different (p<0.05) from control group
[c]Significantly different (p<0.01) from control group

Source: Naylor and Stout 1996

Table A-22. Model Predictions for Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months

Model	Variance p-value[a]	Mean fit p-value[a]	AIC	BMD_{lsd} (mg/kg/day)	$BMDL_{lsd}$ (mg/kg/day)
Linear[b, c]	<0.01	0.42	NA	NA	NA
Linear[c, d]	0.94	<0.01	NA	NA	NA
2-Degree polynomial[c, d]	**0.94**	**0.65**	**215.12**	**15.40**	**12.32**
Power[d]	0.94	0.65	217.11	14.85	7.42

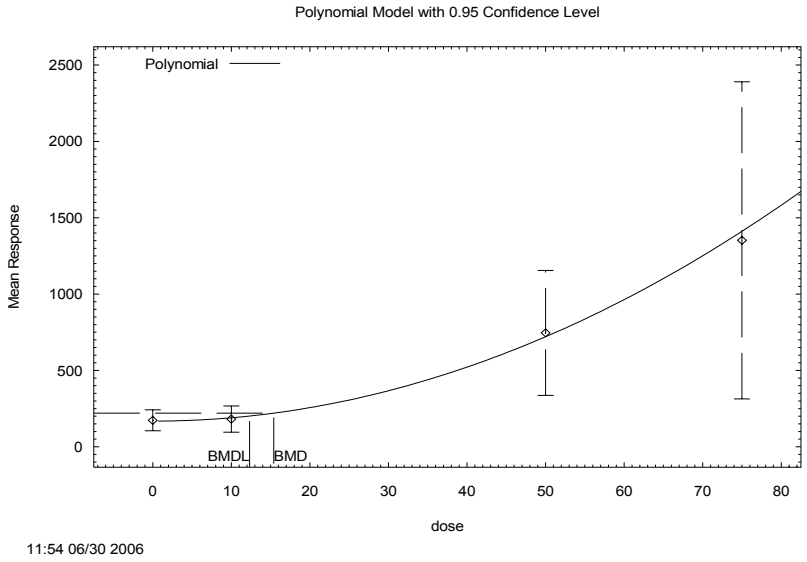
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria
[b]Constant variance assumed
[c]Restriction = non-negative
[d]Nonhomogeneous variance assumed

AIC = Akaike's Information Criteria; BMD_{1sd} = benchmark dose based on a benchmark response of 1 standard deviation above the control mean; $BMDL_{1sd}$ = lower confidence limit (95%) on the BMD_{1sd}; NA = not applicable because model failed a goodness-of-fit test

For the relative liver weight data, the simplest continuous variable model (linear) from the EPA Benchmark Dose Software (Version 1.3.2) was initially fit; constant variance was assumed. A BMR of 1 standard deviation above the control mean was selected in the absence of a biological rationale for using an alternative BMR. The model output indicated that a non-homogeneous variance was more appropriate for the data set (as indicated by a p-value <0.01 for the test for constant variance). However, using non-homogeneous variance, inadequately modeled variance resulted (p-value <0.01). Similar inadequate results were obtained using the more complex polynomial and power models. The Hill model provided inadequate mean fit due to insufficient (0) degrees of freedom. Therefore, the relative liver weight data were judged to be unsuitable for benchmark dose analysis due to inadequate modeling of variance.

For the serum AP data, the simplest continuous variable model (linear) was initially fit; constant variance was assumed. A BMR of 1 standard deviation above the control mean was selected in the absence of a biological rationale for an alternative BMR. The model output indicated that a non-homogeneous variance was more appropriate for the data set (as indicated by a p-value <0.01 for the test for constant variance). However, using non-homogeneous variance, inadequate model mean fit was obtained (p-value <0.01). The more complex (polynomial, power, and Hill) models for continuous data were also fit to the serum AP data. The Hill model provided inadequate mean fit due to insufficient degrees (0) of freedom. Adequate mean fit was obtained with both the 2-degree polynomial and power models. Following conventional protocol for selection of the point of departure (the adequate model with the lowest AIC, the $BMDL_{1sd}$ of 12.32 mg/kg/day (lower 95% confidence limit on the BMD_{1sd} of 15.40 mg/kg/day) was selected as the point of departure for deriving the chronic-duration oral MRL (see Table A-22, Figure A-9). The $BMDL_{1sd}$ of 12.32 mg/kg/day was rounded to one significant figure (10 mg/kg/day), duration adjusted to 7 mg/kg/day, and divided by an uncertainty factor of 100 to derive an MRL of 0.07 mg/kg/day.

Figure A-9. Changes in Serum Alkaline Phosphatase Levels in Female Dogs Orally Exposed to 1,4-Dichlorobenzene for 12 Months*



*BMD and BMDL (in mg/kg/day) are associated with 1 standard deviation above the control mean.

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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 $BMDL_{1sd}$ of 10 mg/kg/day was adjusted to a continuous exposure scenario as follows:

$$BMDL_{1sd\ ADJ} = (BMDL_{1sd})\ (5days/7\ days)$$
$$= (10\ mg/kg/day)\ (5/7)$$
$$= 7\ mg/kg/day$$

Other additional studies or pertinent information that lend support to this MRL: The NOAEL/LOAEL approach to MRL derivation results in the same chronic-duration oral MRL value as the benchmark dose approach. Using the NOAEL of 10 mg/kg/day for increased serum AP and other liver effects in dogs (Naylor and Stout 1996), the NOAEL is duration-adjusted to 7 mg/kg/day (10 mg/kg/day x 5 days/7 days) and divided by the uncertainty factor of 100 to yield an MRL of 0.07 mg/kg/day.

Additional information on the chronic oral effects of 1,4-DCB is available from one study each in rats, mice, and rabbits. Observed effects included nephropathy in rats (including tubular degeneration and atrophy in females) exposed to ≥150 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), hepatocellular degeneration and nephropathy in mice exposed to ≥300 mg/kg/day on 5 days/week for 103 weeks (NTP 1987), and cloudy swelling and minimal focal necrosis in rabbits exposed to 500 mg/kg/day in 263 doses in 367 days (Hollingsworth et al. 1956). The lowest chronic LOAEL in these studies was 150 mg/kg/day for kidney effects in female rats (NTP 1987). Liver and kidney effects were induced in dogs in the principal study (Naylor and Stout 1996) at doses below the LOAELs in the other species.

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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

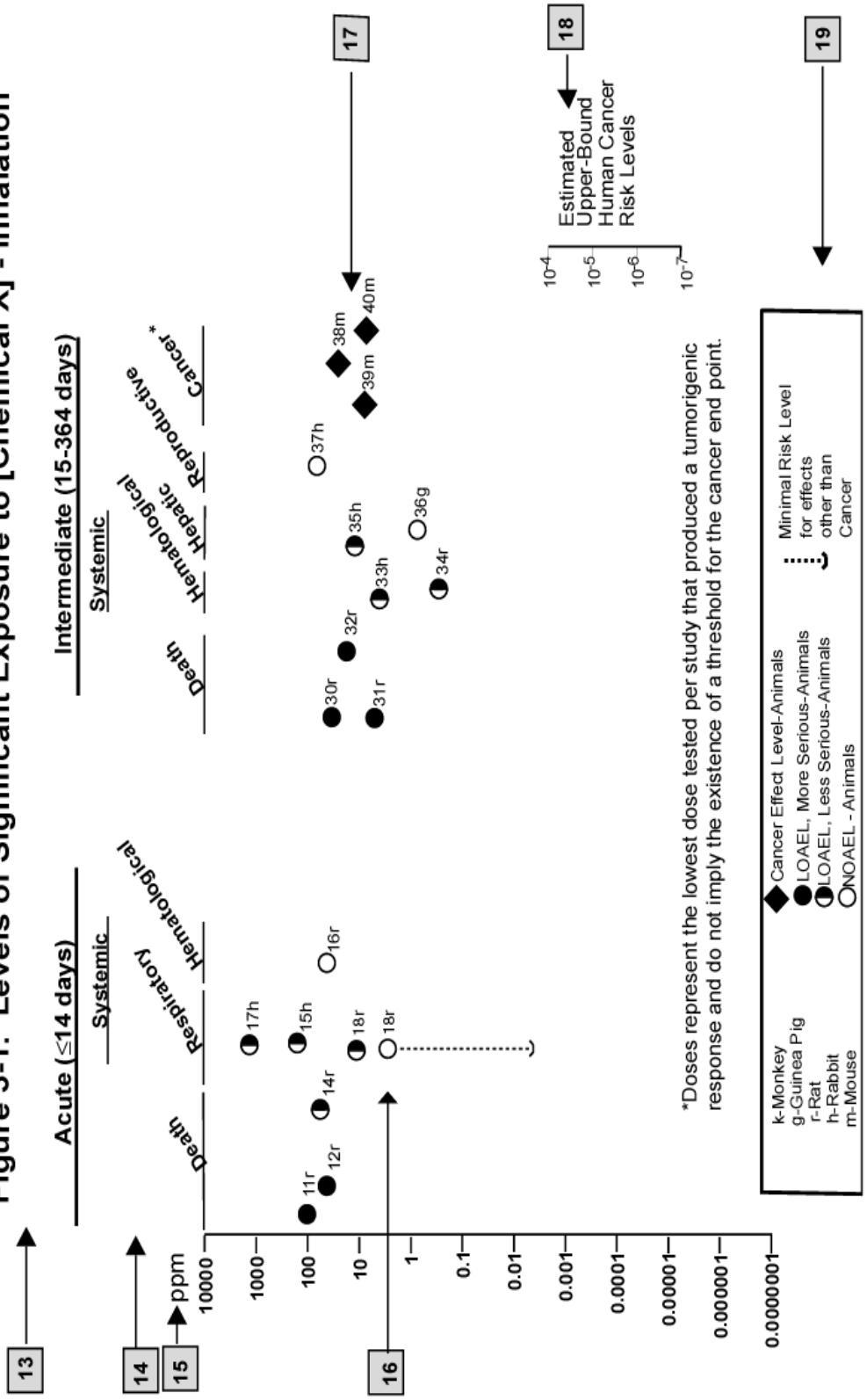
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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 5×10^{-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

APPENDIX C

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