

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, 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,4-Dichlorobenzene (1,4-DCB)
CAS number(s): 106-46-7
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Key to figure: 1
Species: Human

Minimal Risk Level: mg/kg/day ppm mg/m³

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). The medical evaluations included blood cell counts (RBC, WBC, and differential), hemoglobin, hematocrit, mean corpuscular volume, blood urea nitrogen, sedimentation rate, urinalysis, and careful examination of the eyes. Effects of different workplace exposure levels on eye and nose irritation were summarized.

Effects noted in study and corresponding doses: 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 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 [30] 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:

10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? No

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If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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). The current Threshold Limit Value-Time Weighted Average (TLV-TWA) for 1,4-DCB of 10 ppm, which is intended to minimize the potential for eye irritation in exposed workers (ACGIH 2001), is largely based on the human findings of Hollingsworth et al. (1956).

Agency Contact (Chemical Manager): Dr. Malcolm Williams

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Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Key to figure: 13
Species: Rat

Minimal Risk Level: mg/kg/day ppm mg/m³

Reference: Tyl RW, Neepser-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: 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, 5 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 F₁ 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 F₀ 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 F₀ females were continued through mating until sacrifice on gestation day 15. Exposures of the F₀ males continued until sacrificed at the end of the study and satellite mating periods. Groups of 28 F₁ weanlings/sex and satellite groups of 10 F₁ female weanlings were exposed for 11 weeks and mated as described above to produce the F₂ generation. Additionally, 20 F₁ 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 F₀ and F₁ adult (parental) animals, F₁ recovery animals, F₁ weanlings not used in the rest of the study, and F₂ weanlings, and histology was evaluated in the F₀ and F₁ 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 F₀ and F₁ males and females, and gestational, live birth, postnatal survival (4-, 7-, 14-, 21-, and 28-day), and lactation indices were determined for the F₁ and F₂ litters.

Effects noted in study and corresponding doses: There were no effects on reproductive parameters in either generation, although systemic toxicity occurred at all dose levels in F₀ and F₁ adult rats. Hyaline droplet nephropathy was found in F₀ and F₁ 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 F₀ and F₁ adult males and F₁ adult females during the pre-breed exposure periods at 538 ppm. Absolute liver weights were increased in F₀ 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

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211 and 538 ppm groups. In F₀ females, absolute liver weights were increased by 9% in the 211 ppm animals, and 31% in the 538 ppm animals, but only the high-dose animals were statistically significant from controls. Similar changes were seen in relative liver weights of the F₀ 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 F₁ adult males at ≥211 ppm and F₁ adult females at 538 ppm. Hepatocellular hypertrophy was observed in the livers of F₀ and F₁ males and females at 538 ppm; no hepatic histological changes were induced at the lower exposure concentrations. Other effects also occurred in the F₀ and F₁ 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 F₁ and/or F₂ 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) serious LOAELs 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

Dose and end point used for MRL derivation:

[66] NOAEL [] LOAEL

The NOAEL of 66 ppm for increased liver weight in adult rats was selected as the basis for the MRL. As discussed below in the section on other pertinent information, the MRL derived using the NOAEL/LOAEL approach is consistent with an MRL of 0.2 ppm determined using benchmark dose analysis.

Uncertainty factors used in MRL derivation:

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

Although the rat exposure concentration was adjusted to a human equivalent concentration (HEC), an uncertainty factor of 10 was still applied, because 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? NA

Was a conversion used from intermittent to continuous exposure? The NOAEL of 66 ppm was duration-adjusted for the intermittent experimental exposure as follows:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= (\text{NOAEL}) (\text{hours}/24 \text{ hours}) (\text{days}/7 \text{ days}) \\ &= (66 \text{ ppm}) (6/24) (5/7) \\ &= 11.8 \text{ ppm} \end{aligned}$$

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

1,4-DCB exhibited the key effect 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

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of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994). $H_{b/g}$ 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 $NOAEL_{HEC}$ is 11.8 ppm, as follows:

$$\begin{aligned} NOAEL_{HEC} &= (NOAEL_{ADJ}) \times [(H_{b/g})_{RAT} / (H_{b/g})_{HUMAN}], \\ &= 11.8 \text{ ppm} \times [1] = 11.8 \text{ ppm} \end{aligned}$$

The $NOAEL_{HEC}$ was divided by the uncertainty factor of 100 to derive an MRL of 0.1 ppm.

Other additional studies or pertinent information that lend support to this MRL: Information on effects of intermediate-duration inhalation exposure to 1,4-DCB are also 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. 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.

Benchmark dose analysis of data from the Tyl and Neeper-Bradley (1989) study resulted in an MRL of 0.6 ppm, similar to the MRL of 0.1 ppm determined using the $NOAEL/LOAEL$ approach. Benchmark dose analysis was conducted using the data for liver weight in adult male rats and postnatal survival in rat F_1 and F_2 pups, as summarized in Table A-1. Available continuous-variable models in the EPA Benchmark Dose Software (linear, polynomial, power, and Hill models; BMDS version 1.3.2) were fit to the data for changes in liver weight. Adequate fits to the liver weight data, as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS, was obtained with the power model with constant variance assumed. Statistical tests indicated that the homogeneous models provided adequate fits to the data, and that the variance did not warrant fitting the models with non-homogeneous variance functions to the data. To calculate BMCs and BMCLs from the best fitting models, a BMR of a 10% change from control values was selected. Both the power model and the multistage model provided adequate ($p > 0.10$) fits, the model with the lowest AIC, being the power model, was selected. The power model predicted a BMC and BMCL of 171.3 and 138.1 ppm, respectively (Figure A-1).

None of the continuous variable models in the EPA Benchmark Dose Software adequately ($p > 0.1$) fit the F_1 or F_2 survival data as assessed by the chi-square goodness-of-fit statistic. Linear models with either an assumed constant variance or with variance modeled as a power function of the mean were fit to the F_1 pup survival data. Log-likelihood ratio tests indicated that both models adequately described the data, and that a non-homogeneous variance model was more consistent with the data than a constant variance model. Akaike's Information Criteria (AIC) for the non-homogeneous variance model was slightly lower

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than the AIC for the constant variance model, indicating a better fit of the data. The non-homogeneous variance model (Figure A-1) was therefore selected to calculate the benchmark concentration (BMC) and the lower 95% confidence limits (BMCL) for reduced 4-day survival in F₁ rat pups, using a 5% decrease in pup survival index (compared with the control) as the benchmark response (BMR). A 5% decrease was selected (instead of 10% or 1 standard deviation change from the control), because the effect (decreased postnatal survival) is severe and one that would be of high concern if it occurred in human populations. The BMC and BMCL are 146 and 93 ppm, respectively, which are similar to the values based on the liver weight data.

The BMCL of 138 ppm was selected as the point of departure for the MRL. To calculate the MRL, the BMCL of 138 ppm is first duration-adjusted for intermittent exposure, as follows (EPA 1994k):

$$\begin{aligned} \text{BMCL}_{\text{ADJ}} &= (\text{BMCL}) (\text{hours}/24 \text{ hours}) (\text{days}/7 \text{ days}) \\ &= (138 \text{ ppm}) (6/24) (5/7) \\ &= 24.6 \text{ ppm} \end{aligned}$$

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 MRL. The human equivalent concentration (HEC) for extrapulmonary effects produced by a category 3 gas is calculated by multiplying the duration-adjusted BMCL 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_{HEC} becomes 16.6 ppm:

$$\begin{aligned} \text{BMCL}_{\text{HEC}} &= (\text{BMCL}_{\text{ADJ}}) \times [(H_{b/g})_{\text{RAT}} / (H_{b/g})_{\text{HUMAN}}], \\ &= 24.6 \text{ ppm} \times [1] = 24.6 \text{ ppm} \end{aligned}$$

The BMCL_{HEC} was divided by an uncertainty factor of 100 to derive the MRL. This uncertainty factor is comprised of component factors of 10 for interspecies extrapolation and 10 for human variability. As described above, despite the use of a dosimetric adjustment to account for differences between rats and humans, a default factor of 10 was applied. Dividing the 24.6 ppm BMCL_{HEC} for increased liver weight by the uncertainty factor of 100 yields an MRL of 0.2 ppm.

Table A-1. Selected Effects in Rats Exposed to 1,4-Dichlorobenzene by Inhalation for Two Generations (Tyl and Neeper-Bradley 1989)

Effect	Exposure concentration (ppm)			
	0	66	211	538
Relative liver weight in F ₀ adult males (mean ± SD)	3.465±0.2328 (n=27)	3.631 ^a ±0.2080 (n=28)	3.945 ^b ±0.259 2 (n=28)	5.271 ^b ±0.2474 (n=27)
4-Day survival index ^c in F ₁ pups [mean ± SD (no. litters)]	93.8±20.33 (n=24)	97.5±3.57 (n=20)	92.7±21.07 (n=27)	82.0 ^a ±29.25 (n=22)
4-Day survival index ^c in F ₂ pups [mean ± SD (no. litters)]	99.1±2.25 (n=22)	99.4±2.80 (n=20)	99.3±1.99 (n=24)	71.3 ^a ±41.96 (n=21)

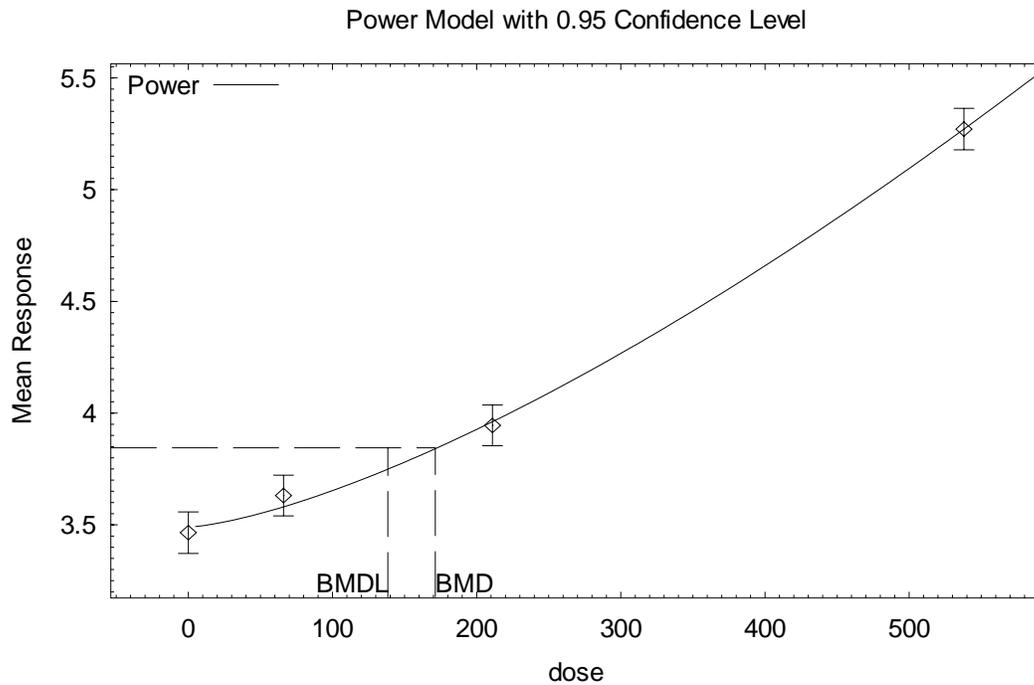
^aSignificantly different (p<0.05) from control group as reported by study investigators.

^bSignificantly different (p<0.01) from control group as reported by study investigators.

^c4-Day survival index = number of pups surviving 4 days ÷ total number of live pups at birth.

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Figure A-1. Observed Liver Weights in Adult Male Rats Exposed to 1,4-Dichlorobenzene for Two Generations and Predicted Liver Weights by the Power Model



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Key to figure: 31
Species: Rat

Minimal Risk Level: mg/kg/day [0.02] ppm mg/m³

Reference: 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:BDF1 mice were exposed 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. Various other effects also occurred in rats at 300 ppm, including changes in organ weights (liver in both sexes, kidneys in males) and 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), but a lack of both numerical data and statistical analysis precludes interpretations of significance for these end points. Additional findings included histopathological changes in the kidneys and nasal epithelia. The kidney lesions occurred only in male rats at 300 ppm and included significantly increased incidences of mineralization of the renal papilla and in hyperplasia of the urothelium. The nasal lesions mainly included increased incidences of eosinophilic changes 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 28/50, 29/50, 39/50, and 47/50 in females. The increases were statistically significant ($p \leq 0.05$, Fisher's Exact Test performed by ATSDR) and there was a trend of increasing response with increasing dose in both sexes (Cochran-Armitage test performed by ATSDR). Additionally observed were significantly increased incidences of eosinophilic changes of the respiratory epithelium and respiratory metaplasia in 300 ppm females, and an increase in mineralization of the renal papilla in 300 ppm males.

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 slightly reduced in male mice at all levels of exposure, but the decreases were

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not significantly different from controls or significantly dose-related ($p > 0.05$, Fisher's Exact and Cochran-Armitage tests performed by ATSDR). Survival in exposed females was comparable to controls. Terminal body weights were reduced at 300 ppm in both males (≈ 10 – 15% less than controls, beginning at study week 80) and females (≈ 7 – 10% less than controls, beginning at study week 84). Various other effects also occurred in the 300 ppm mice, including changes in organ weights (increased liver weights in both sexes, increased kidney and decreased ovary weights in females) and hematology 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), but a lack of reported numerical data and results of statistical analysis precludes interpretation of these end points. Additional findings included histopathological changes in male liver and testes. The incidence of centrilobular hepatocellular hypertrophy was significantly increased in male mice at 300 ppm (0/49, 0/49, 0/50, 34/49), and the incidence of mineralization of the testis was significantly increased in male mice at ≥ 75 ppm (27/49, 35/49, 42/50, 41/49). No nonneoplastic histological changes were observed in female mice.

Dose and end point used for MRL derivation:

NOAEL LOAEL

As the lesions are considered to be sensitive signs of cellular degeneration, nasal olfactory lesions in female rats were selected as the critical effect; the LOAEL for this effect was 74.8 ppm. The NOAEL of 19.8 ppm for nasal olfactory epithelial lesions (of moderate or greater severity) was selected as the basis for the MRL. As discussed below in the section on other pertinent information, the MRL of 0.02 ppm derived using the NOAEL/LOAEL approach is consistent with an MRL of 0.01 ppm determined using benchmark dose analysis based on the incidence of moderate or severe changes in the nasal olfactory epithelium.

Uncertainty factors used in MRL derivation:

 3 for extrapolation from animals to humans
 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.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? The chronic NOAELs of 19.8 ppm for nasal olfactory epithelial lesions in rats and 19.9 ppm for testicular mineralization in mice were considered for MRL derivation. The animal NOAELs were duration-adjusted for intermittent experimental exposure, as follows:

Rat:	NOAEL _{ADJ}	=	(NOAEL) (hours/24 hours) (days/7 days)
		=	(19.8 ppm) (6/24) (5/7)
		=	3.54 ppm

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$$\begin{aligned}
 \text{Mouse: NOAEL}_{\text{ADJ}} &= (\text{NOAEL}) (\text{hours}/24 \text{ hours}) (\text{days}/7 \text{ days}) \\
 &= (19.9 \text{ ppm}) (6/24) (5/7) \\
 &= 3.55 \text{ ppm}
 \end{aligned}$$

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Human equivalent concentrations (HECs) were calculated using EPA (1994a) inhalation dosimetric adjustment methodology to determine which of the NOAELs is the most appropriate basis for the MRL. For the olfactory epithelium changes in 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:

$$\begin{aligned}
 \text{RGDR}_{\text{ET}} &= [(V_{\text{E}}/SA_{\text{ET}})_{\text{A}}/(V_{\text{E}}/SA_{\text{ET}})_{\text{H}}] \\
 &= (0.24 \text{ m}^3/\text{day}/15\text{cm}^2)/(20 \text{ m}^3/\text{day}/200\text{cm}^2) \\
 &= 0.16 \\
 \text{where: RGDR}_{\text{ET}} &= \text{regional gas deposition ratio in the extrathoracic region} \\
 V_{\text{E}} &= \text{minute volume in rats } (V_{\text{E}})_{\text{A}} \text{ or humans } (V_{\text{E}})_{\text{H}} \\
 SA_{\text{ET}} &= \text{extrathoracic surface area in rats } (SA_{\text{ET}})_{\text{A}} \text{ or humans } (SA_{\text{ET}})_{\text{H}}
 \end{aligned}$$

The rat $\text{NOAEL}_{\text{ADJ}}$ was multiplied by the RGDR_{ET} to yield a NOAEL HEC of 0.57 ppm, as follows:

$$\begin{aligned}
 \text{NOAEL}_{\text{HEC}} &= \text{NOAEL}_{\text{ADJ}} \times \text{RGDR}_{\text{ET}} \\
 &= 3.54 \text{ ppm} \times 0.16 \\
 &= 0.57 \text{ ppm}
 \end{aligned}$$

For the testicular lesions in mice, 1,4-DCB exhibited the effect outside of the respiratory tract and consequently is treated as a category 3 gas for purposes of calculating the HEC. The HEC for extrathoracic effects produced by a category 3 gas is calculated by multiplying the duration-adjusted LOAEL by the ratio of blood:gas partition coefficients ($H_{\text{b/g}}$) in animals and humans (EPA 1994). $H_{\text{b/g}}$ 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 $\text{NOAEL}_{\text{HEC}}$ is 3.55 ppm, as follows:

$$\begin{aligned}
 \text{NOAEL}_{\text{HEC}} &= (\text{NOAEL}_{\text{ADJ}}) \times [(H_{\text{b/g}})_{\text{MOUSE}} / (H_{\text{b/g}})_{\text{HUMAN}}], \\
 &= 3.55 \text{ ppm} \times [1] = 3.55 \text{ ppm}
 \end{aligned}$$

As derived above, the HECs corresponding to the NOAELs for the nasal lesions in rats and testicular lesions in mice are 0.57 and 3.55 ppm, respectively. The lower of these $\text{NOAEL}_{\text{HEC}}$ values, 0.57 ppm, was selected as the basis for the MRL.

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.

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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, and the occurrence of nasal and testicular effects in rats and mice at concentrations similar to or lower than those that caused nasal lesions in rats and testicular lesions in mice. Although the available 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, and were adequate to derive the acute inhalation MRL.

Benchmark dose analysis of data from the Japan Bioassay Research Center (1995) study resulted in an MRL of 0.01 ppm, similar to the MRL of 0.02 ppm determined using the NOAEL/LOAEL approach. Benchmark dose analysis was conducted using the incidences for eosinophilic changes of moderate or greater severity in the nasal olfactory epithelium in female rats, the incidences for mineralization of the testis in male mice, and the actual exposure concentrations in each species (Table A-2). All dichotomous models in the Benchmark Dose Software (version 1.3.2) were fit to both sets of incidence data. For the nasal lesions in female rats, as assessed by the chi-square goodness-of-fit statistic, all models provided adequate fits to the data. As assessed by Aikake's Information Criteria (AIC), the log-probit model provided the best fit to the rat data (Table A-3a, Figure A-2). Using a benchmark response level (BMR) of 10% extra risk above the control incidence, the log-probit model resulted in a benchmark concentration (BMC_{10}) of 24.22 ppm and lower 95% confidence limit ($BMCL_{10}$) of 15.34 ppm. For the testicular lesions in mice, as assessed by the chi-square goodness-of-fit statistic and AIC, the log-logistic model was the only model that adequately fit the data (Table A-3b). Using a BMR of 10% extra risk above the control incidence, the log-probit model resulted in a BMC_{10} of 11.90 ppm and $BMCL_{10}$ of 4.82 ppm.

The animal $BMCL_{10}$ values of 15.34 ppm (rat nasal lesions) and 4.82 ppm (mouse testicular lesions) were duration-adjusted for intermittent experimental exposure, as follows:

$$\begin{aligned} \text{Rat nasal lesions: } \quad BMCL_{10 \text{ ADJ}} &= (BMCL_{10}) (\text{hours}/24 \text{ hours}) (\text{days}/7 \text{ days}) \\ &= (15.34 \text{ ppm}) (6/24) (5/7) \\ &= 2.74 \text{ ppm} \end{aligned}$$

$$\begin{aligned} \text{Mouse testicular lesions: } \quad BMCL_{10 \text{ ADJ}} &= (BMCL_{10}) (\text{hours}/24 \text{ hours}) (\text{days}/7 \text{ days}) \\ &= (4.82 \text{ ppm}) (6/24) (5/7) \\ &= 0.86 \text{ ppm} \end{aligned}$$

For the 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):

$$\begin{aligned} RGDR_{ET} &= [(V_E/SA_{ET})_A / (V_E/SA_{ET})_H] \\ &= (0.24 \text{ m}^3/\text{day}/15\text{cm}^2) / (20 \text{ m}^3/\text{day}/200\text{cm}^2) \\ &= 0.16 \\ \text{where: } RGDR_{ET} &= \text{regional gas deposition ratio in the extrathoracic region} \\ V_E &= \text{minute volume in rats } (V_E)_A \text{ or humans } (V_E)_H \\ SA_{ET} &= \text{extrathoracic surface area in rats } (SA_{ET})_A \text{ or humans } (SA_{ET})_H \end{aligned}$$

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The HEC was calculated by multiplying the rat $BMCL_{10\ ADJ}$ by the $RGDR_{ET}$ to yield a $BMCL_{10\ HEC}$ of 0.44 ppm, as follows:

$$\begin{aligned} BMCL_{10\ HEC} &= BMCL_{10\ ADJ} \times RGDR_{ET} \\ &= 2.74\ \text{ppm} \times 0.16 \\ &= 0.44\ \text{ppm} \end{aligned}$$

For the testicular changes in male mice, 1,4-DCB exhibited the effects outside of the respiratory tract and is treated as a category 3 gas for purposes of calculating the HEC. The HEC for extra respiratory effects produced by a category 3 gas is calculated by multiplying the mouse $BMCL_{10\ ADJ}$ by the ratio of blood:gas partition coefficients ($H_{b/g}$) in animals and humans (EPA 1994). $H_{b/g}$ values were not available for 1,4-DCB in mice and humans. Using a default value of 1 for the ratio of partition coefficients, the $BMCL_{10\ HEC}$ is 4.82 ppm, as follows:

$$\begin{aligned} BMCL_{10\ HEC} &= (BMCL_{10\ ADJ}) \times [(H_{b/g})_{RAT} / (H_{b/g})_{HUMAN}] \\ &= 0.86\ \text{ppm} \times 1 \\ &= 0.86\ \text{ppm} \end{aligned}$$

Because the $BMCL_{10\ HEC}$ value for nasal effects in rats is lower than that based on testicular effects in mice, the rat data were selected to derive the MRL. The $BMCL_{10\ HEC}$ of 0.44 ppm for nasal effects in rats was divided by the uncertainty factor of 30 to derive an MRL of 0.01 ppm.

Table A-2. Selected Effects in Rats and Mice Exposed to 1,4-Dichlorobenzene by Inhalation for 104 weeks (Japan Bioassay Research Center 1995)

Rat, female	Exposure concentration (ppm)	0	19.8	74.8	298.4
	Nasal olfactory epithelial lesions (incidence) ^a	28/50 ^b	29/50	39/50 ^c	47/50 ^c
Mouse, male	Exposure concentration (ppm)	0	19.9	74.8	298.3
	Mineralization of testes (incidence)	27/49	35/49	42/50 ^c	41/49 ^c

^aLesions of moderate or greater severity.

^bSignificant trend of increasing response with increasing dose (Cochran-Armitage Test, performed by ATSDR).

^cSignificantly ($p \leq 0.05$) different from control value (Fisher's Exact Test performed by ATSDR).

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Table A-3a. Modeling Results for Incidences of Nasal Olfactory Epithelial Lesions in Female Rats Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Model	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)	x ² p-value	AIC
gamma ^a	14.48	9.72	0.70	216.75
Logistic	19.65	13.99	0.54	217.26
Log-logistic ^b	17.34	4.43	0.66	218.20
Multi-stage ^c	14.48	9.72	0.70	216.75
Probit	22.35	16.76	0.46	217.62
Log-probit^b	24.22	15.34	0.83	216.37
Quantal linear	14.48	9.72	0.70	216.75
Quantal quadratic	67.93	53.42	0.12	220.42
Weibull ^a	14.48	9.72	0.70	216.75

^aRestrict power ≥1

^bSlope restricted to >1

^cRestrict betas ≥0; Degree of polynomial=3

Table A-3b. Modeling Results for Incidences of Mineralization of Testes in Male Mice Exposed to 1,4-Dichlorobenzene by Inhalation for 104 Weeks

Model	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)	x ² p-value	AIC
gamma ^a	1.45	0.00	NA	176.02
Logistic	38.71	23.63	0.04	224.50
Log-logistic^b	11.90	4.82	0.11	221.91
Multi-stage ^c	31.72	18.02	0.04	224.07
Probit	41.79	26.57	0.03	224.66
Log-probit ^b	60.53	30.61	0.02	225.81
Quantal linear	31.72	18.02	0.04	224.07
Quantal quadratic	116.39	82.82	0.01	226.96
Weibull	31.72	18.02	0.04	224.07

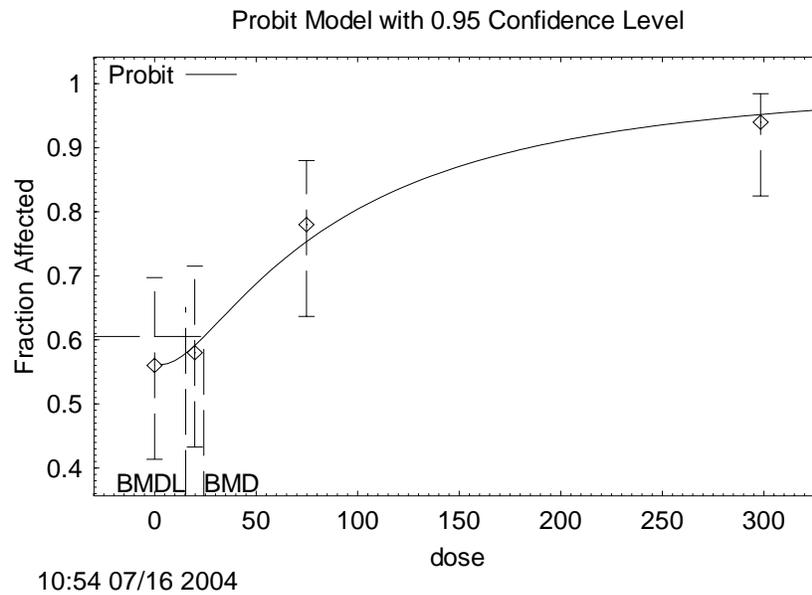
^aRestrict power ≥1

^bSlope restricted to >1

^cRestrict betas ≥0; Degree of polynomial=3

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



Agency Contact (Chemical Manager): Dr. Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,2-Dichlorobenzene (1,2-DCB)
CAS number(s): 95-50-1
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Key to figure: 11
Species: Rat

Minimal Risk Level: [0.8] mg/kg/day ppm mg/m³

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 LD₅₀ 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 group 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 (Robinson et al. 1991). 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. 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 other groups not reported but assumed to be 0/10). Incidences of other hepatic lesions were not significantly increased, but included inflammation (characterized by lymphocyte and macrophage infiltrates) and degeneration of hepatocytes (characterized varying degrees of fibrillar or vacuolated cytoplasm and swelling with intact cell membranes). This study identified a NOAEL of 75 mg/kg/day and minimal 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.

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Dose and end point used for MRL derivation:

NOAEL LOAEL

The 75 mg/kg/day NOAEL for increased liver weight (Robinson et al. 1991) was used as the basis for the MRL. As discussed below in the section on other pertinent information, the MRL of 0.8 mg/kg/day derived using the NOAEL/LOAEL approach is consistent with an MRL of 0.4 mg/kg/day determined using benchmark dose analysis.

Uncertainty factors used in MRL derivation:

10 for extrapolation from animals to humans

10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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.

Benchmark dose analysis was conducted using liver effects data from the 10-day Robinson et al. (1991) study. Dichotomous or continuous variable models available in the EPA Benchmark Dose Software were fit to data for: (1) incidences of liver necrosis in male rats, (2) changes in serum ALT in both sexes, and (3) changes in liver weight, as summarized in Table A-4. For the dichotomous variable end point (incidences of liver necrosis), Akaike's Information Criteria (AIC) was used to select the best fitting model from which benchmark doses (BMDs) and their lower 95% confidence limits (BMDLs) were calculated, using a BMR of 10% extra risk. For the continuous variable end points (changes in serum ALT and liver weight), BMDs and BMDLs were calculated using one standard deviation above the control mean as the BMR. The best fit was provided by the female rat liver weight data and polynomial model, which yielded the lowest BMD₁₀ and BMDL₁₀ values of 52.2 and 36.1 mg/kg/day, respectively (Table A-5, Figure A-3). The BMDL of 36.1 mg/kg/day was divided by the uncertainty factor of 100 to derive an MRL of 0.4 mg/kg/day.

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Table A-4. Liver Effects Observed in Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days (Robinson et al. 1991)

Effects	Sex	Dose (mg/kg/day)				
		0	37.5	75	150	300
Liver necrosis (incidence)	M	0/10 ^a	0/10 ^a	0/10 ^a	0/10 ^a	4/10 ^b
	F	0/10 ^a	0/10 ^a	0/10 ^a	0/10 ^a	0/10 ^a
Mean serum ALT (IU/L)	M	47±6 n=10	49±8 n=10	54±7 n=10	60±13 n=10	71±14 ^b n=9
	F	39±5 n=10	37±7 n=10	38±7 n=10	46±10 n=10	57±14 n=10
Mean serum cholesterol (mg/dL)	M	78.4±8.7 n=10	73.5±10.4 n=10	66.2±17.1 n=10	74.7±16.2 n=10	58.1±28.1 n=9
	F	79.3±11.4 n=10	100.6±11.4 n=10	98.3±13.0 ^b N=10	99.5±15.2 ^b n=10	100.3±10.2 ^b n=10
Liver weight (g)	M	9.8±0.70 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

^aIncidences of liver necrosis were only reported for the male 0 and 300 mg/kg/day dose groups. Incidences of this lesion in the other male and all female groups are assumed to be 0/10 each.

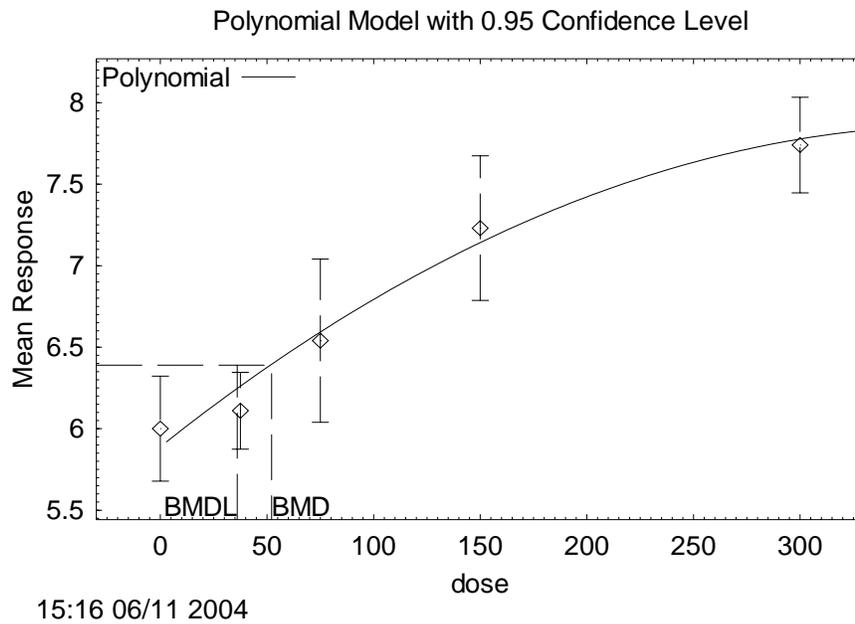
^bSignificantly ($p \leq 0.05$) different from control value.

Table A-5. BMD Modeling Results for Changes in Liver Weight in Female Rats Orally Exposed to 1,2-Dichlorobenzene for 10 Days

Model	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)	AIC-fitted
Linear	84.67	67.73	-11.85
Linear-nonhomogeneous	82.44	56.39	-7.87
Polynomial	52.19	36.06	-12.73
Polynomial-nonhomogeneous	50.12	31.82	-8.78
Power	84.67	67.73	-7.85
Power-nonhomogeneous	82.44	56.39	-5.87
Hill	71.51	43.18	-10.55
Hill-nonhomogeneous	67.46	failed	-8.76

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Figure A-3. Observed Liver Weights in Female Rats Exposed to 1,2-Dichlorobenzene for 10 Days and Predicted Liver Weights by the Polynomial Model



Agency Contact (Chemical Manager): Dr. Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,2-Dichlorobenzene (1,2-DCB)
CAS number(s): 95-50-1
Date: September 16, 2004
Profile status: Pre Public Comments Draft 3
Route: [] Inhalation [X] Oral
Duration: [] Acute [X] Intermediate [] Chronic
Key to figure: 17
Species: Rat

Minimal Risk Level: [0.4] mg/kg/day [] ppm [] mg/m³

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 B6C3F₁ mice were administered 1,2-dichlorobenzene (>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 89.3 and 179 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 8, 17, and 45% in males in the 125, 250, and 500 mg/kg/day groups, respectively, and 8, 15, and 30% in females in the 125, 250, and 500 mg/kg/day groups, respectively; increased relative liver weights were not seen at lower doses of 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. 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 seen in both sexes at 125 mg/kg/day are believed to represent the beginning of adverse hepatic effects, despite their small magnitude, 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

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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 BMCL

The 60 mg/kg/day NOAEL for increased liver weight in rats was used as the basis for the MRL. As discussed below in the supporting information section, the MRL of 0.4 mg/kg/day derived using the NOAEL/LOAEL approach is consistent with an MRL of 0.2 mg/kg/day determined using benchmark dose analysis.

Uncertainty factors used in MRL derivation:

10 for extrapolation from animals to humans
 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? Yes. The NOAEL of 60 mg/kg/day was duration-adjusted using a factor of 5/7 (representing 5 days of exposure for every 7-day week) to give an adjusted NOAEL of 42.9 mg/kg/day. The MRL was derived by applying an uncertainty factor of 100 to the adjusted NOAEL.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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 subchronic 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.

Benchmark Dose analysis was conducted using the rat and mouse liver lesion incidence data summarized in Table A-6. 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 rats and mice of both sexes. For each data set, Akaike's Information Criteria (AIC) was used to select the best fitting model from which benchmark doses (BMDs) and their lower 95% confidence limits (BMDLs) were calculated, using a BMR of 10% extra risk. The best fit was provided by the female rat

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liver lesion data and quantal-linear model, which yielded the lowest BMD₁₀ and BMDL₁₀ values of 32.6 and 21.3 mg/kg/day, respectively (Table A-7, Figure A-4). The BMDL₁₀ was divided by the uncertainty factor of 100 to derive an MRL of 0.2 mg/kg/day.

Table A-6. Incidence of Liver Lesions in Rats and Mice Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks (NTP 1985)

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	0/10	4/10 ^a	9/10 ^a
Male mouse	0/10	ND	ND	0/10	0/10	9/10 ^a

^aSignificantly ($p < 0.05$) different from control; Fisher Exact Test performed by ATSDR.

ND = no histological examinations conducted in this group

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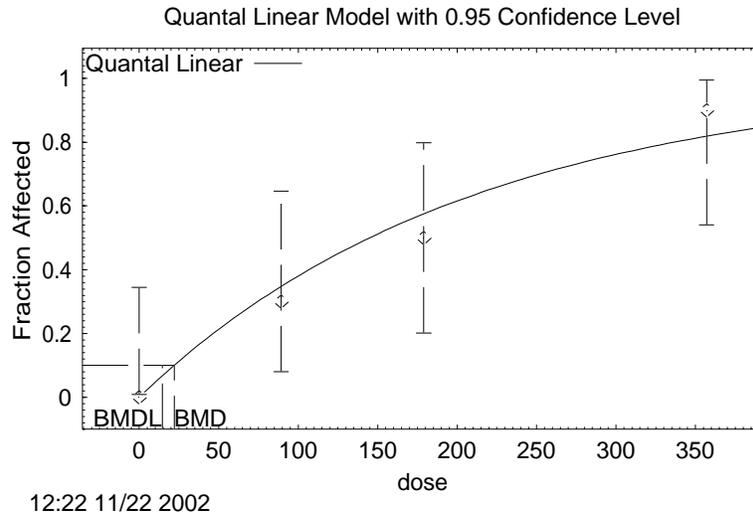
Table A-7. BMD Modeling of Incidence Data for Liver Lesions in Male and Female Rats and Male Mice Exposed to 1,2-Dichlorobenzene (NTP 1985). BMDs and BMDLs were Calculated Based on a BMR of 10% Extra Risk for the Lesion

Model	AIC	Chi-square p-value	BMD ^a (mg/kg/day)	BMDL ^a (mg/kg/day)
Male rats				
Gamma	32.996	0.941	82.23	25.22
Logistic	32.910	0.983	85.66	31.71
Multi-stage (3-degree)	33.155	0.869	76.72	24.62
Probit	32.895	0.990	87.18	42.53
Quantal-linear	33.001	0.612	31.86	20.41
Quantal-quadratic	31.207	0.952	86.05	68.07
Weibull	33.105	0.893	76.27	24.80
Female rats				
Gamma	36.875	0.864	44.25	15.30
Logistic	37.181	0.744	51.54	10.45
Multi-stage (3-degree)	36.638	0.972	30.27	15.60
Probit	37.120	0.765	53.90	27.56
Quantal-linear	35.428	0.855	22.04	14.66
Quantal-quadratic	36.009	0.638	68.49	54.77
Weibull	36.806	0.893	41.67	15.38
Male mice				
Gamma	24.770	0.755	123.44	73.16
Logistic	24.605	0.812	125.59	78.97
Multi-stage (4-degree)	25.525	0.280	119.51	48.20
Probit	24.408	0.860	126.07	82.05
Quantal-linear	30.420	0.136	31.98	20.44
Quantal-quadratic	26.569	0.692	83.38	65.53
Weibull	25.450	0.611	113.78	61.86

^aDuration-adjusted doses were modeled.

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Figure A-4. Observed Incidences of Liver Lesions in Female Rats Exposed to 1,2-Dichlorobenzene for 13 Weeks and Incidences Predicted by the Quantal-linear Model



Agency Contact (Chemical Manager): Dr. Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,2-Dichlorobenzene (1,2-DCB)
CAS number(s): 95-50-1
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Key to figure: 31
Species: Mouse

Minimal Risk Level: [0.4] mg/kg/day ppm mg/m³

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 B6C3F₁ mice were administered 1,2-dichlorobenzene (>99% pure) in corn oil by gavage in doses of 0, 60, or 120mg/kg 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-exposure 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 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.

Dose and end point used for MRL derivation:

[60] NOAEL [120] LOAEL

The 60 mg/kg/day NOAEL for increased incidence of renal tubular regeneration was used as the basis for the MRL. As discussed below in the supporting information section, the MRL of 0.4 mg/kg/day derived using the NOAEL/LOAEL approach is consistent with an MRL of 0.3 mg/kg/day determined using benchmark dose analysis.

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Uncertainty factors used in MRL derivation:

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

The NOAEL of 60 mg/kg/day for increased incidence of renal tubular regeneration in male mice from the NTP (1985) study was duration-adjusted, as described below, to a NOAEL_{ADJ} of 43 mg/kg/day. The MRL of 0.4 mg/kg/day was derived by dividing the NOAEL_{ADJ} by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). It is noteworthy that this value is the same as that for the intermediate-duration MRL.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? Because exposure occurred only 5 days/week, the NOAEL was duration-adjusted as follows:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= (\text{NOAEL}) (5 \text{ days}/7 \text{ days}) \\ &= (60 \text{ mg/kg/day}) (5/7) \\ &= 43 \text{ mg/kg/day} \end{aligned}$$

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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 exposure to 1,2-dichlorobenzene.

Benchmark dose analysis was conducted using the mouse kidney lesion incidence data summarized in Table A-8. Dichotomous models available in the EPA Benchmark Dose Software were fit to data for incidences of renal tubule regeneration in male mice. For each data set, Akaike's Information Criteria (AIC) was used to select the best fitting model from which benchmark doses (BMDs) and their lower 95% confidence limits (BMDLs) were calculated, using a BMR of 10% extra risk. The best fit was provided by the logistic model, which yielded BMD₁₀ and BMDL₁₀ values of 45.0 and 30.7 mg/kg/day, respectively (Table A-9, Figure A-5). The BMDL₁₀ was divided by the uncertainty factor of 100 to derive an MRL of 0.3 mg/kg/day.

Table A-8. Incidence of Liver Lesions in Rats and Mice Orally Exposed to 1,2-Dichlorobenzene for 13 Weeks (NTP 1985)

Lesions: regeneration of kidney tubule cells	Dose (mg/kg/day)		
	0	60	120
Male mouse	8/48	12/50	17/49 ^a

^aSignificantly (p<0.05) different from control; Fisher Exact Test performed by ATSDR.

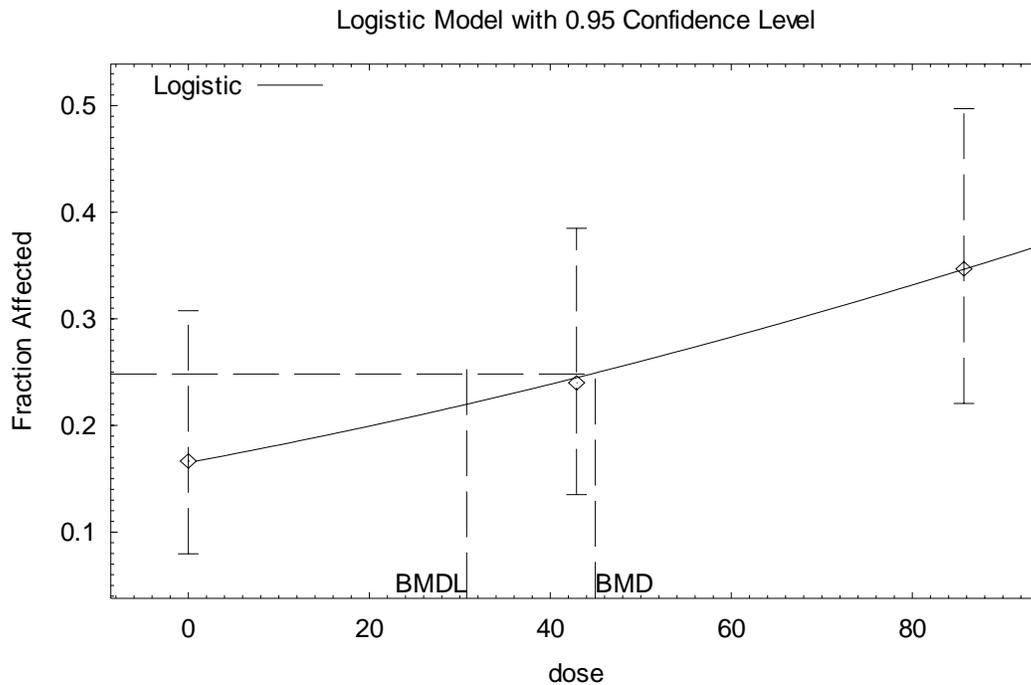
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Table A-9. BMD Modeling of Incidence Data for Renal Lesions in Male Mice Exposed to 1,2-Dichlorobenzene (NTP 1985). BMDs and BMDLs were Calculated Based on a BMR of 10% Extra Risk for the Lesion

Model	AIC	Chi-square p-value	BMD ^a (mg/kg/day)	BMDL ^a (mg/kg/day)
Gamma	167.624	1.00	47.1	21.3
Logistic	165.630	0.9375	45.0	30.7
Multi-stage (2-degree)	167.624	1.00	47.1	21.3
Probit	165.636	0.9135	44.0	29.4
Quantal-linear	165.711	0.7688	38.5	21.1
Quantal-quadratic	165.729	0.7446	56.6	40.8
Weibull	167.624	1.00	47.2	21.3

^aDuration-adjusted doses were modeled.

Figure A-5. Observed Incidences of Kidney Lesions in Male Mice Exposed to 1,2-Dichlorobenzene for 13 Weeks and Incidences Predicted by the Logistic Model



Agency Contact (Chemical Manager): Dr. Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,3-Dichlorobenzene (1,3-DCB)
CAS number(s): 541-73-1
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: [] Inhalation [X] Oral
Duration: [X] Acute [] Intermediate [] Chronic
Key to figure: 2
Species: Rat

Minimal Risk Level: [0.4] mg/kg/day [] ppm [] mg/m³

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 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 organ weight changes included significantly increased liver weight in males at ≥ 147 mg/kg/day and in females at ≥ 368 mg/kg/day, 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

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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 (minimal) based on the liver weight increase in male rats. The NOAEL for increased liver weight is 37 mg/kg/day.

Dose and end point used for MRL derivation:

[37] NOAEL [147] LOAEL

The 37 mg/kg/day NOAEL for increased liver weight in rats was used as the basis for the MRL. As discussed below in the supporting information section, benchmark dose analysis of the liver weight data resulted in an MRL value that is similar to that derived using the NOAEL/LOAEL approach (i.e., 0.5 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? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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

Benchmark dose analysis was conducted using liver effects data summarized in Table A-10. Dichotomous or continuous variable models available in the EPA Benchmark Dose Software were fit to data for: (1) incidences of hepatocellular degeneration in male and female rats, (2) changes in serum ALT in male rats, and (3) changes in liver weight. For the dichotomous variable end point (incidences of hepatocellular degeneration), Akaike's Information Criteria (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 continuous variable end points (changes in serum ALT and liver weight), BMDs and BMDLs were calculated using a 10% change from the control mean as the BMR. The best fit was provided by the female rat liver weight data and polynomial-nonhomogeneous model, which yielded the lowest BMD and BMDL values of 61.1 and 45.9 mg/kg/day, respectively (Table A-11, Figure A-6). The BMDL of 45.9 mg/kg/day was divided by an uncertainty factor of 100 to derive an MRL of 0.5 mg/kg/day.

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Table A-10. 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
Centrolobular 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
Mean serum ALT (IU/L)	M	35.5±7.3 n=10	33.0±9.8 n=10	39.9±10.8 n=10	39.0±6.9 n=9	81.7±79.1 ^b n=10
	F	32.1±6.0 n=8	35.5±7.3 n=10	36.7±12.5 n=9	42.3±9.3 n=10	43.6±10.6 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
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

Source: McCauley et al. 1995

^aIncidences of centrolobular 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.

^bSignificantly ($p \leq 0.05$) different from control value.

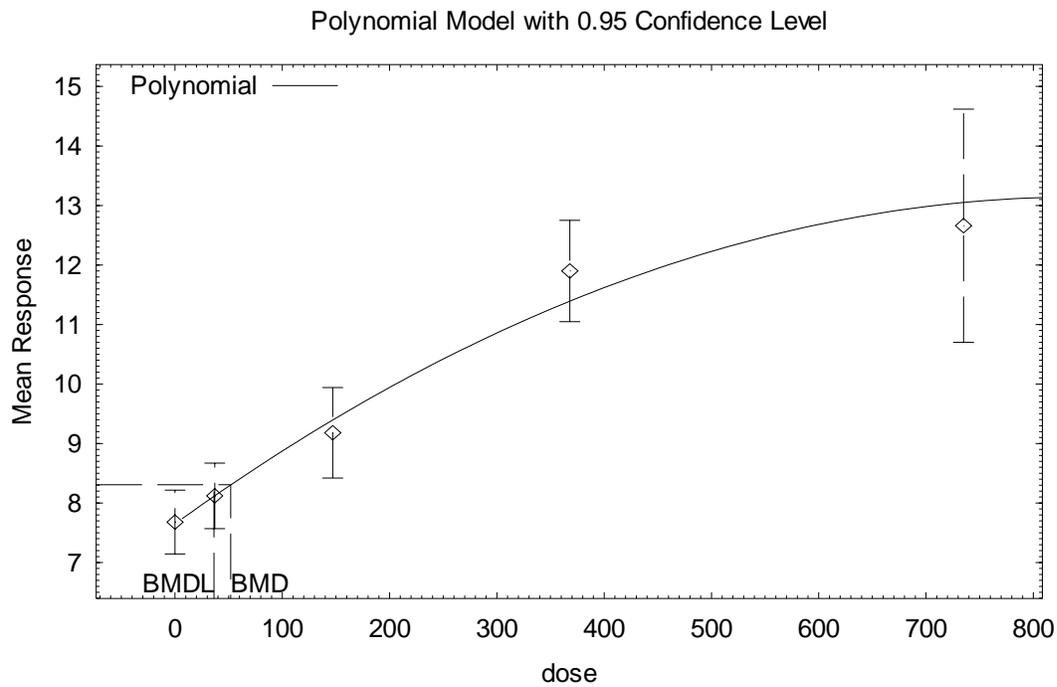
Table A-11. Change in Liver Weight in Female Rats Orally Exposed to 1,3-Dichlorobenzene for 10 Days

Model	BMD (mg/kg/day)	BMDL (mg/kg/day)	AIC-fitted
Linear	113.64	91.46	88.82
Linear-nonhomogeneous	87.74	71.96	68.39
Polynomial	50.46	36.80	81.46
Polynomial-nonhomogeneous	61.13	45.93	66.05
Power	113.64	91.46	92.82
Power-nonhomogeneous	87.74	F	70.39
Hill	92.90	35.98	82.74
Hill-nonhomogeneous	78.99	F	67.87

F = computation failed in model fitting program

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Figure A-6. Observed Liver Weights in Female Rats Exposed to 1,3-Dichlorobenzene for 10 Days and Predicted Liver Weights by the Polynomial Nonhomogeneous Model



09:59 09/09 2004

Agency Contact (Chemical Manager): Dr. Malcolm Williams

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,3-Dichlorobenzene (1,3-DCB)
CAS number(s): 541-73-1
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: [] Inhalation [X] Oral
Duration: [] Acute [X] Intermediate [] Chronic
Key to figure: 7
Species: Rat

Minimal Risk Level: [0.03] mg/kg/day [] ppm [] mg/m³

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 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 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).

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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.

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.

Dose and end point used for MRL derivation:

[] NOAEL [9] LOAEL

The 9 mg/kg/day minimal LOAEL for thyroid lesions was used as the basis for the MRL. As discussed below in the supporting information section, benchmark dose analysis of the thyroid data resulted in an MRL value that is the same as that derived using the NOAEL/LOAEL approach (i.e., 0.03 mg/kg/day).

Uncertainty factors used in MRL derivation:

- [X] 3 for extrapolation from a minimal LOAEL to a NOAEL
- [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? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

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

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Benchmark dose analysis was conducted using the thyroid and pituitary lesion incidence data summarized in Table A-12. 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, Akaike's Information Criteria (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, the Gamma, Multi-stage, Quantal-linear, and Weibull models provided a better fit than other models in the BMD software (Table A-13). The chi-square goodness-of-fit statistics for all of these models indicated poor statistical fits across all of the models ($p < 0.1$), but a graph of the observed incidences of thyroid lesions and Gamma-model predicted incidences show a reasonable visual fit (Figure A-7). Therefore, the BMDL₁₀ predicted from the Gamma model, 1.9 mg/kg/day, was selected as the best BMDL₁₀ for thyroid lesions in male rats.

For the pituitary cytoplasmic vacuolation incidence data, the Gamma, Quantal-linear, and Weibull models provided a nearly equivalent fit as the Probit model, using the AIC as the fit indicator (Table A-13, Figure A-8). The BMD₁₀ and BMDL₁₀ from the Gamma model were 4.08 and 2.10 mg/kg/day, whereas the BMD₁₀ and BMDL₁₀ from the Probit model were 7.79 and 4.46 mg/kg/day. Given the similarities of these BMDL₁₀ values, their average, 3.3 mg/kg/day, was selected as the BMDL₁₀ for pituitary cytoplasmic vacuolation in male rats.

Due to the similarity of the BMDL₁₀ values for thyroid lesions (1.9 mg/kg/day) and pituitary lesions (3.3 mg/kg/day), the average of these values, 2.6 mg/kg/day, was selected as the point of departure for the MRL. The BMDL₁₀ of 2.6 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 0.03 mg/kg/day.

Table A-12. Incidence of Thyroid and Pituitary Lesions Observed in Male Rats Orally Exposed to 1,3-Dichlorobenzene for 90 Days

Lesion	Dose (mg/kg/day)				
	0	9	37	147	588
Thyroid, reduced follicular colloidal density	2/10	8/10 ^a	10/10 ^a	8/9 ^a	8/8 ^a
Pituitary, cytoplasmic vacuolation in pars distalis	2/10	6/10	6/10	10/10 ^a	7/7 ^a

Source: McCauley et al. 1995

^aSignificantly ($p < 0.05$) different from control; Fisher Exact Test performed by ATSDR

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Table A-13. BMD Modeling of Incidence Data for Thyroid and Pituitary Lesions in Male Rats Exposed to 1,3-Dichlorobenzene for 90 Days; BMDs and BMDLs were Calculated Based on a BMR of 10% Extra Risk for the Lesion

Model	AIC	Chi-square p-value	BMD ₁₀ (mg/kg-day)	BMDL ₁₀ (mg/kg-day)
Thyroid, reduced follicular colloidal density				
Logistic	44.630	0.006	8.02	3.83
Gamma	42.974	0.002	4.09	1.90
Multi-stage (4 degree)	42.974	0.002	4.09	1.90
Probit	45.202	0.006	10.61	5.986
Quantal-linear	42.974	0.002	4.09	1.90
Quantal-quadratic	47.644	0.002	38.87	22.76
Weibull	42.974	0.002	4.09	1.90
Pituitary, cytoplasmic vacuolation in pars distalis				
Gamma	43.466	0.4887	4.08	2.1
Logistic	43.58	0.4639	7.49	4.29
Multi-stage (4-degree)	45.056	0.3466	5.23	2.23
Probit	43.442	0.4823	7.79	4.46
Quantal-linear	43.466	0.4887	4.08	2.1
Quantal-quadratic	44.122	0.376	17.11	10.10
Weibull	43.466	0.4887	4.08	2.1

Source: McCauley et al. 1995

Figure A-7. Observed Incidences of Thyroid Lesions in Male Rats Exposed to 1,3-Dichlorobenzene for 90 Days and gamma-model Predicted Incidences

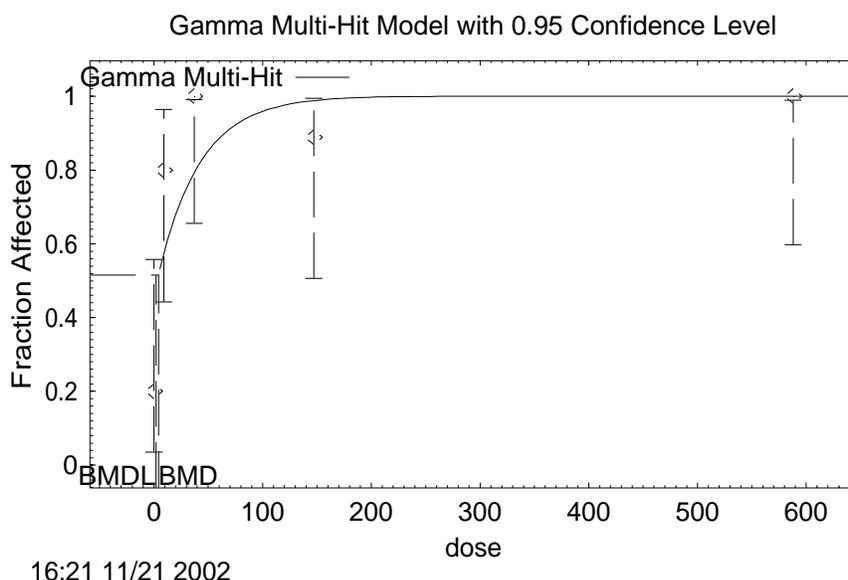
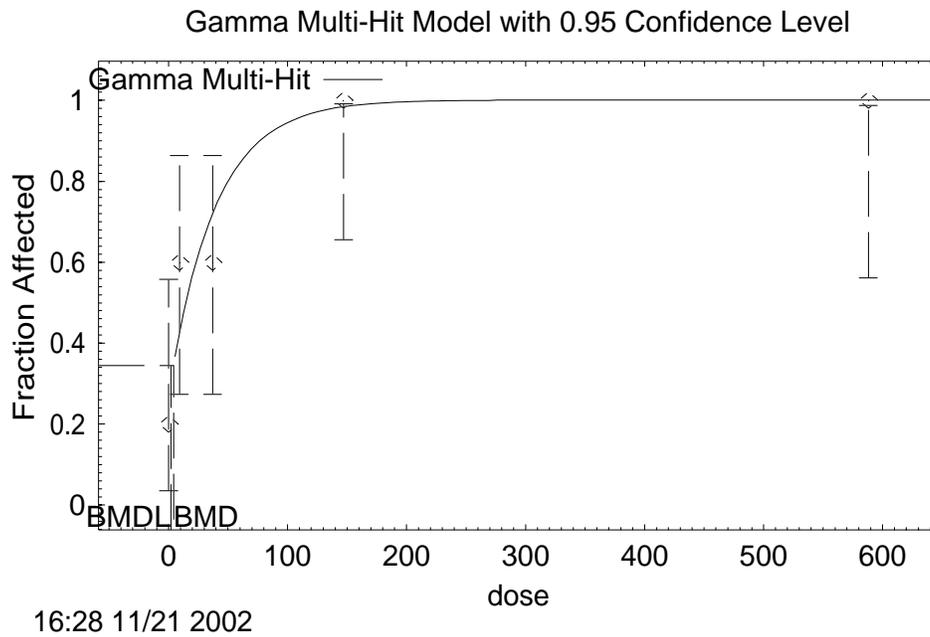


Figure A-8. Observed Incidences for Pituitary Lesions in Male Rats and Incidences Predicted by the gamma Model



Agency Contact (Chemical Manager): Dr. Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: 1,4-Dichlorobenzene (1,4-DCB)
CAS number(s): 106-46-7
Date: September 16, 2004
Profile status: Pre-Public Comments Draft 3
Route: [] Inhalation [X] Oral
Duration: [] Acute [X] Intermediate [] Chronic
Key to figure: 45
Species: Dog

Minimal Risk Level: [0.07] mg/kg/day [] ppm [] mg/m³

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. (As cited in EPA 1996b).

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. Study end points included clinical observations, body weight, food consumption, ophthalmoscopic examination, hematology (11 indices, including activated partial thromboplastin time, at months 6 and 12), clinical chemistry (18 indices, including ALT, AST, GGTP, AP, and creatinine phosphokinase, at months 6 and 12), urinalysis (10 indices), organ weights, gross pathology, and histology.

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 (Naylor and Stout 1996). 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 levels of enzymes included significantly increased AP (50 mg/kg/day males, and 50 and 75 mg/kg/day females, at months 6 and 12), ALT (75 mg/kg/day females at month 12),

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and GGTP (75 mg/kg/day females at months 6 and 12), and significantly decreased albumin (50 and 75 mg/kg/day in males at months 6 and 12, and 75 mg/kg/day females at month 6). Absolute and relative liver weights were significantly increased 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 (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 an unspecified number of males at 50 and 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:

[10] NOAEL [50] LOAEL

The NOAEL of 10 mg/kg/day for hepatic effects was used as the basis for the MRL.

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? NA (capsule study)

Was a conversion used from intermittent to continuous exposure? The NOAEL of 10 mg/kg/day was adjusted to a continuous exposure scenario as follows:

$$\begin{aligned} \text{NOAEL}_{\text{ADJ}} &= (\text{NOAEL}) (\text{days}/7 \text{ days}) \\ &= (10 \text{ mg/kg/day}) (5/7) \\ &= 7.1 \text{ mg/kg/day} \end{aligned}$$

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA

Other additional studies or pertinent information that lend support to this MRL: Available information on the MRL study is limited to an EPA Data Evaluation Record (DER) summary. A benchmark dose-based MRL could be considered pending acquisition and review of the original Monsanto Company report (MRID# 43988802).

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,

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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 other species based on increases in liver weight, serum enzymes, and histopathology following exposure to doses as low as 50 mg/kg/day for 1 year 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 $\alpha 2\mu$ -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 F₁ pups and increased total number of deaths from birth to postnatal day 4 in F₁ and F₂ 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 F₁ and F₂ pups, reduced neurobehavioral performance (draw-up reflex evaluated at weaning) in F₂ pups, and increased relative liver weight in adult F₁ 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 and kidney effects were induced by exposure to doses as low as 50 mg/kg/day for 1 year (Naylor and Stout 1996), which are below subchronic LOAELs of approximately 150–200 mg/kg/day for these

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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 F₁ and F₂ pups, at doses ≥ 90 mg/kg/day (Bornatowicz et al. 1994). Although this finding indicates that perinatal developmental toxicity is an additional sensitive end point for 1,2-DCB exposure, the lower 50 mg/kg/day hepatotoxicity LOAEL in dogs (Naylor and Stout 1996) is a more appropriate basis for MRL derivation.

Agency Contact (Chemical Manager): Dr. Malcolm Williams

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

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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.

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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,

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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/m³ 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.

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- (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

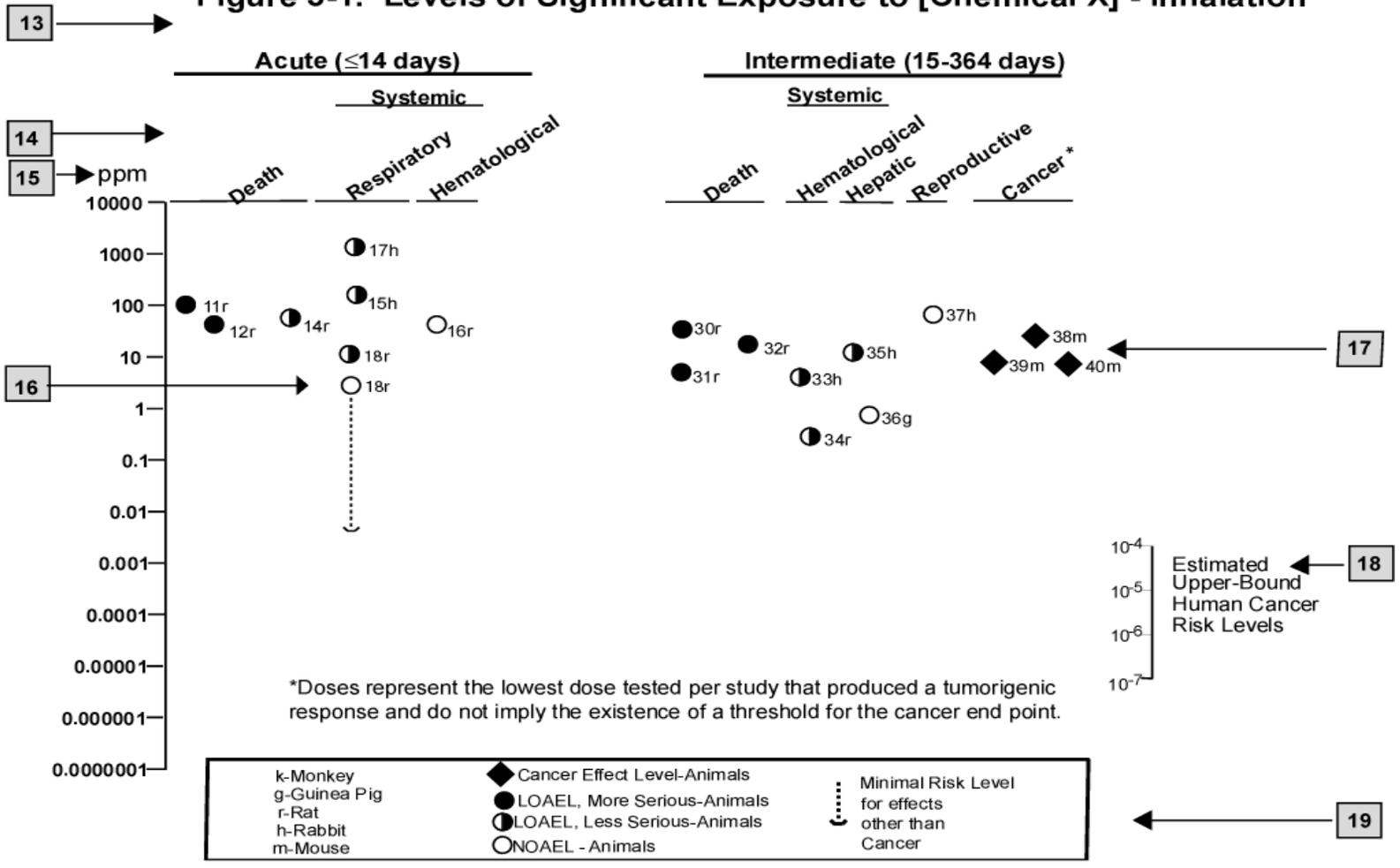
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → ^a The number corresponds to entries in Figure 3-1.
^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 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



DRAFT FOR PUBLIC COMMENT

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

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DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International 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
K _d	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	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

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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

APPENDIX C

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

APPENDIX C

>	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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