APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 5
Species: Rat

Minimal Risk Level: 0.01 [ ] mg/kg/day [X] mg/m^3

Reference: Hartman HR. 1990. 21-Day repeated exposure inhalation toxicity in the rat. EPA guidelines no. 82-4. Laboratory study number 891205. Ciba-Geigy Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41557402.

Experimental design: Four groups of albino rats (10/sex) were exposed (nose only) to aerosols of diazinon (in ethanol) at concentrations of 0, 0.05, 0.46, 1.57, or 11.6 mg/m^3 for 6 hours/day, 5 days/week for 3 weeks. Particle size analysis was performed to ensure that the test aerosols were in the respirable range for the rat. Two control groups were used, one exposed to humidified filtered air only and the other to the carrier vehicle ethanol. The test substance was the liquid MG-8 formulation (88% diazinon). Exposure levels were monitored by gas chromatography. Clinical examinations included ophthalmology, body weight, food consumption, hematology, and blood chemistry (including plasma ChE and RBC AChE activity). At necropsy, organ weights and brain AChE activity were assessed and histopathological examinations were performed on nasal tissues and lungs from all groups and on the spleen, heart, liver, kidney, adrenal gland, and any tissue with gross lesions from the control and 11.6 mg/m^3 groups.

Effect noted in study and corresponding doses: No deaths or changes in body weights or food consumption were observed. Piloerection was noted in most animals, particularly during the first week of exposure, the incidence gradually declining during weeks 2 and 3 of exposure. This sign was neither exposure- nor dose-related and no clinical signs of organophosphate toxicity were observed. No exposure-related ophthalmoscopic or histopathological lesions were found. There were no statistically significant exposure-related effects on hematological parameters, although minimally lower values for erythrocyte count, hemoglobin, and packed red cell volume were observed in female rats of the highest exposure level. A significantly higher lung-to-body weight ratio was observed in female rats of the 0.46 and 1.57 mg/m^3 exposure levels, but not at the highest exposure level. The toxicological significance of this effect is uncertain because no histopathological evidence of exposure-related lung lesions was found. As shown in Table A-1, significant reductions in plasma ChE (marker for exposure) were seen in males at exposure levels $\geq$1.57 mg/m^3 and females at exposure levels $\geq$0.46 mg/m^3. Organophosphate-induced plasma ChE inhibition is typically observed at exposure levels lower than those inducing measurable RBC or brain AChE inhibition. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. In the principal study (Hartman 1990), significant reductions in RBC AChE activity (surrogate marker for neural AChE activity) were seen in male rats at 11.6 mg/m^3 and in female rats at 1.57 and 11.6 mg/m^3 (Table A-1). Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). The 10% RBC AChE inhibition observed in the 1.57 mg/m^3 group of female rats is below the level of inhibition considered to represent an adverse effect. Therefore, the 1.57 mg/m^3 exposure level is a

NOAEL and the highest exposure level (11.6 mg/m^3) is the lowest-observed-adverse-effect level (LOAEL) for 36 and 39% RBC AChE inhibition in the male and female rats, respectively. There was no significant difference between brain AChE activity in any of the exposure groups of male rats and that of vehicle controls. All diazinon-exposed groups of female rats exhibited significantly decreased brain AChE activity, relative to vehicle controls. The report of significantly increased brain AChE inhibition in the female rats of all exposure levels is indicative of an inherent problem with the brain data set, perhaps related to tissue collection or quantitative analysis of enzymatic activity in the brain tissue of the female rats. Furthermore, results of repeated oral dosing (Singh 1988) indicate that the male and female rats are comparably sensitive to diazinon-induced effects on both RBC and brain AChE activity. Therefore, the report (Hartman 1990) of significant brain AChE inhibition in the female rats exposed to diazinon by inhalation at levels much lower than the LOAEL of 11.6 mg/m^3 for RBC AChE inhibition is questionable and a clear LOAEL for brain AChE inhibition cannot be determined.

Table A-1. Relative Change (Percent of Control Values) in Cholinesterase Activities in Male and Female Rats Following Exposure to Aerosols of Diazinon for 90 Days

	Plasma ChE	RBC AChE	Brain AChE
Male rats			
0.05 mg/m^3	+9%[a]	+2%	-1%
0.46 mg/m^3	-5%	-5%	+1%
1.57 mg/m^3	-14%[b]	-6%	-4%
11.6 mg/m^3	-19%[b]	-36%[a]	-3%
Female rats			
0.05 mg/m^3	-3%	-1%	-24%[a]
0.46 mg/m^3	-20%[b]	+6%	-17%[b]
1.57 mg/m^3	-27%[a]	-10%[b]	-20%[b]
11.6 mg/m^3	-43%[a]	-39%[a]	-37%[a]

[a]statistically significantly different from control (p≤0.01)
[b]statistically significantly different from control (p≤0.05)

AChE = acetylcholinesterase; ChE = cholinesterase; RBC = red blood cell

Source: Hartman 1990

Dose and end point used for MRL derivation: A NOAEL of 1.57 mg/m^3; the LOAEL was 11.6 mg/m^3 for 36–39% RBC AChE inhibition in male and female rats of the principal study

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL of 1.57 mg/m^3 was adjusted for intermittent exposure as follows:

$NOAEL_{ADJ}$ = 1.57 mg diazinon/m^3 x 6 hours/24 hours x 5 days/7 days = 0.28 mg diazinon/m^3

A regional deposited dose ratio ($RDDR_{ER}$) of 1.558 for extrarespiratory effects was used to extrapolate from rats to humans. The $RDDR_{ER}$ was calculated using EPA's software (Version 2.3) (EPA 1994b) for calculating RDDRs and the parameters listed in Table A-2.

Table A-2. Parameters[a] Used to Calculate the Regional Deposited Dose Ratio ($RDDR_{ER}$) for Diazinon-induced Extrarespiratory Effects Using EPA's Software (Version 2.3)

Biological parameters[b]	Rat	Human
Surface area		
Extrathoracic	15 cm^2	200 cm^2
Tracheobronchial	22.5 cm^2	3,200 cm^2
Pulmonary	0.34 m^2	54 m^2
Minute ventilation	147.24 mL	13.8 L
Body weight	196 g	70 kg

[a]Mass Median Aerodynamic Diameter (MMAD) = 0.85 µm from lower limit of 0.8 µm and upper limit of 0.9 µm for the 1.57 mg/m^3 exposure group of female rats reported by Hartman (1990); Geometric Standard Deviation (GSD) = 1.3 µm from lower limit of 1.2 µm and upper limit of 1.4 µm reported by Hartman (1990).
[b]Parameters are default values for rats and humans from the EPA software, except for the rat body weight which was the mean body weight for the 1.57 mg/m^3 exposure group of female rats.

Source: Hartman 1990

The human equivalent concentration was calculated using Equation 4-5 (EPA 1994b) as follows:

$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x $RDDR_{ER}$ = 0.28 mg diazinon/m^3 x 1.558 = 0.44 mg diazinon/m^3

The $NOAEL_{HEC}$ of 0.44 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 0.01 mg/m^3.

Was a conversion used from intermittent to continuous exposure? Yes.

Other additional studies or pertinent information that lend support to this MRL: This is the only available well-conducted, intermediate-duration inhalation study for diazinon. In an acute-duration study in which rats were exposed to 2,300 mg/m^3 diazinon for 4 hours (Holbert 1989), mild signs of organophosphate toxicity were noted (nasal discharge, salivation).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.006 [X] mg/kg/day [ ] mg/m^3

Reference: Davies DB, Holub BJ. 1980a. Toxicological evaluation of dietary diazinon in the rat. Arch Environ Contam Toxicol 9(6):637-650.

Experimental design: Groups of female Wistar rats (50/group) were exposed to diazinon (99.2% purity) in the diet at concentrations of 0, 5, 10, or 15 ppm for 92 days. Interim assessments of neurological end points included treatment day 12 assessment, which represents acute-duration oral exposure. Blood samples were collected on treatment days 3, 8, and 12 from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Other groups of similarly-treated rats were sacrificed (n=6) for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. The study authors reported starting mean body weight (0.139 kg), mean body weight gain (0.00163 kg/day), and mean food consumption (0.0178 kg/day) for all rats, and indicated that they did not significantly differ among treatment groups. Using the average body weight gain for 12 days (0.00163 kg/day x 12 days=0.02 kg), the average body weight for the 12-day period was equal to the starting body weight (0.139 kg) plus one-half the body weight gain during the 12-day period (0.5x0.02 kg)=0.149 kg. The diazinon dose equals the product of the diazinon concentration in food times the mean daily food consumption divided by the average body weight. Calculated in this manner, the doses to the 5-, 10-, and 15-ppm exposure groups were 0.6, 1.2, and 1.8 mg/kg/day, respectively.

Effect noted in study and corresponding doses: No clinical signs of toxicity were observed in any of the treated groups. Compared to controls, significant plasma ChE inhibition was observed in all diazinon-treated groups at all timepoints (including treatment days 3, 8, and 12). At treatment day 12, treatment-related effects included 43, 70, and 73% plasma ChE inhibition and 5, 22, and 33% RBC AChE inhibition in the 0.6, 1.2, and 1.8 mg/kg/day dose groups, respectively. There was no significant effect on brain AChE activity. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. However, inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity. The principal study (Davies and Holub 1980a) identified a NOAEL of 0.6 mg/kg/day and a LOAEL of 1.2 mg/kg/day for 22% RBC AChE inhibition at interim day 12 assessment of female rats administered diazinon in the diet for 92 days.

Dose and end point used for MRL derivation: A NOAEL of 0.6 mg/kg/day; the LOAEL was 1.2 mg/kg/day for 22% RBC AChE inhibition

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated from reported mean values for initial body weight, food consumption, and body weight gain for the first 12 days of treatment.

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

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

Other additional studies or pertinent information that lend support to this MRL: In an unpublished study (EPA 1996), male and female rats were administered diazinon in the diet for 28 days and assessed for cholinesterase inhibition at weeks 1, 2, and 4. A dose of 2.4 mg/kg/day resulted in 38–59% RBC AChE inhibition in both males and females, which was observed as early as week 1 and peaked at week 2. The next lower dose (0.02 mg/kg/day) represented a NOAEL. The principal study for deriving the acute-duration oral MRL for diazinon (Davies and Holub 1980a) was performed using only female rats. However, Davies and Holub (1980a) noted that dietary studies in their laboratory had demonstrated that female rats were more sensitive than male rats to diazinon induced plasma ChE and RBC and brain AChE inhibition. In light of this finding, the selection of RBC AChE inhibition in the female rats as the critical effect from the principal study that assessed the critical effect only in female rats (Davies and Holub 1980a) is appropriate.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Diazinon
CAS number(s): 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 63
Species: Rat

Minimal Risk Level: 0.002 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Davies DB, Holub BJ. 1980a. Toxicological evaluation of dietary diazinon in the rat. Arch Environ Contam Toxicol 9(6):637-650.

Note: Available intermediate-duration oral (dietary) toxicity studies of diazinon include 10 studies in rats and 2 studies in dogs (see Table A-4, page A-14, for a summary of NOAELs and LOAELs for RBC and brain AChE inhibition identified in these studies). Although dose spacing is variable, and in some studies may be in excess of 100-fold for levels at or below identified LOAELs for AChE inhibition, these studies collectively indicate that the threshold for less serious AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg/kg/day. The report of Davies and Holub (1980a) includes results from separate 35-, 42-, and 92-day studies.

Experimental design: In the principal study, groups of female Wistar rats (16/group) were exposed to diazinon (99.2% purity) in the diet at concentrations of 0, 1, 2, 3, or 4 ppm for 42 days (Davies and Holub 1980a). Blood samples were collected periodically from 10 rats/group for assessment of plasma ChE and RBC AChE activity. Six rats per group were sacrificed on day 35 for assessment of brain AChE activity. All rats were assessed daily for clinical signs of neurotoxicity and body weights and food intake were monitored throughout the treatment period. The study authors stated that female rats were used in the study because they were noted to be more sensitive than male rats to the neurotoxic effects of diazinon. The study authors reported starting mean body weight (0.149 kg), mean body weight gain (0.00259 kg/day), and mean food consumption (0.0178 kg/day) for all rats, and indicated that they did not significantly differ among treatment groups. Using the average body weight gain for 42 days (0.00259 kg/day x 42 days=0.11 kg), the average body weight for the 42-day period was equal to the starting body weight (0.149 kg) plus one-half the body weight gain during the 42-day period (0.5x0.11 kg)=0.2 kg. The diazinon dose equals the product of the diazinon concentration in food times the mean daily food consumption divided by the average body weight. Calculated in this manner, the doses to the 1-, 2-, 3-, and 4-ppm exposure groups were 0.09, 0.18, 0.27, and 0.36 mg/kg/day.

Effects noted in study and corresponding doses: No clinical signs of toxicity were observed in any of the treated groups (Davies and Holub 1980a). Significant plasma ChE inhibition was observed at most timepoints in all diazinon-treated groups, relative to controls. The magnitude of inhibition in all treatment groups increased with time and appeared to peak around day 35, remaining near the peak level for the remaining 7 treatment days. Maximum plasma ChE inhibition in the 1, 2, 3, and 4 ppm treatment groups was approximately 35, 50, 55, and >60%, respectively. Plasma ChE inhibition is used as an indicator of exposure, but does not serve as a reliable indicator of a neurotoxic effect. Therefore, plasma ChE inhibition was not considered relevant to the selection of the critical effect for diazinon. Through treatment day 35, there was no significant treatment-related effect on RBC AChE activity in any of the treatment groups. However, on treatment day 42, significant RBC AChE inhibition was observed at

treatment levels of 2, 3, and 4 ppm (magnitude 9, 20, and 22%, respectively). There were no indications of treatment-related significant brain AChE inhibition at any timepoint during the 42 days of treatment. The results of RBC AChE activity in the female rats of the principal study (Davies and Holub 1980a) are presented in Table A-3. Inhibition of RBC AChE and brain AChE represents a relevant neurological effect. Treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity. The principal study (Davies and Holub 1980a) identified a NOAEL of 0.18 mg/kg/day and a LOAEL of 0.27 mg/kg/day for 20% RBC AChE inhibition in female rats administered diazinon in the diet for 42 days.

Table A-3. RBC AChE Data From Female Rats Exposed to Diazinon in the Diet for 42 Days

Dose group (mg/kg/day)	Number of rats	RBC AChE activity (µmole/mL packed cells/minute)	Percent RBC AChE inhibition
0	10	0.74±0.05[a]	
0.09	10	0.68±0.07	8
0.18	10	0.67±0.06	9
0.27	10	0.59±0.04	20
0.36	10	0.58±0.02	22

[a]Mean±standard error

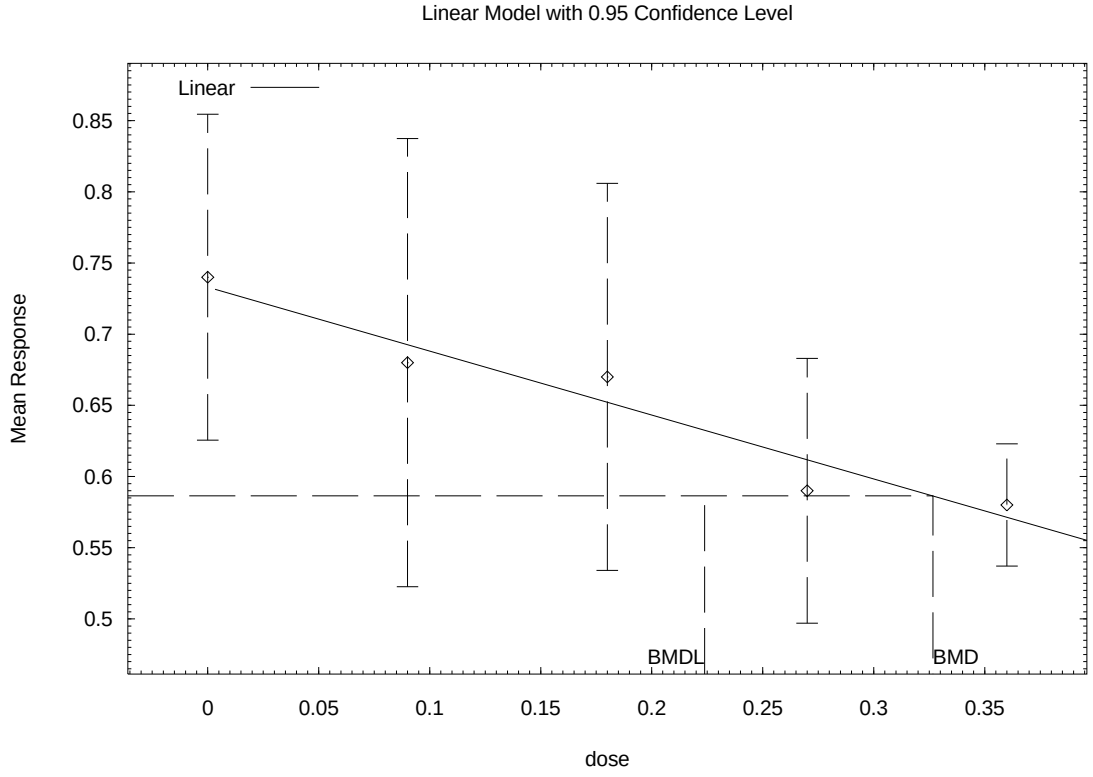
AChE = acetylcholinesterase; RBC = red blood cell

Source: Davies and Holub 1980a

The linear model in the EPA Benchmark Dose Software (Version 1.3.2) was fit to the female rat data for RBC AChE activity shown in Table A-3. A benchmark response (BMR) of 20% below the control mean RBC AChE activity was selected because treatment-related 20–59% RBC or brain AChE inhibition is considered to represent a less serious adverse effect in the absence of more clear indicators of neurotoxicity (Chou and Williams-Johnson 1998). Although the linear model provided adequate fit to the data from Table A-3, as indicated by acceptable p values for tests for (1) differences in response and/or variances among dose levels, (2) homogeneous or non-homogeneous variance, and (3) model mean fit, a non-homogeneous variance model run was suggested. Adequate fit was also provided by the linear model using non-homogeneous variance, which resulted in a BMD_{20} of 0.3267 mg/kg/day and a $BMDL_{20}$ of 0.2238 mg/kg/day. Because the simplest model, the linear model, provided adequate fit to the RBC AChE data from the 42-day rat study of Davies and Holub (1980a), the application of more complex continuous variable models was not considered necessary. The $BMDL_{20}$ of 0.2238 mg/kg/day served as the point of departure for deriving an intermediate-duration oral MRL for diazinon.

Figure A-1 is a plot of predicted and observed levels of RBC AChE activity in the female dogs of the principal study (Davies and Holub 1980a) generated from the linear model using non-homogeneous variance.

Figure A-1. Predicted and Observed Levels of RBC AChE Activity in Female Dogs Orally Exposed to Diazinon for 42 Days*



*BMD and BMDL (in mg/kg/day) are associated with a benchmark response of 20% reduction in RBC AChE activity from the control value

The linear model form and parameters output from benchmark dose analysis of RBC AChE activity in the female rats of the principal study (Davies and Holub 1980a) follows:

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The form of the response function is:

   Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

   Dependent variable = MEAN
   Independent variable = dose
   Signs of the polynomial coefficients are not restricted
   The variance is to be modeled as Var(i) = alpha*mean(i)^rho

   Total number of dose groups = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
```

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Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	0.02612
rho =	0
beta_0 =	0.734
beta_1 =	-0.455556

Variable	Parameter Estimates Estimate	Std. Err.	95.0% Wald ConfidenceInterval Lower Conf. Limit	Upper Conf. Limit
alpha	0.729698	0.927763	-1.08868	2.54808
rho	8.31	2.91288	2.60086	14.0191
beta_0	0.73306	0.0466142	0.641698	0.824422
beta_1	-0.448823	0.162678	-0.767667	-0.129979

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	rho	beta_0	beta_1
alpha	1	0.99	-0.049	0.064
rho	0.99	1	-0.053	0.068
beta_0	-0.049	-0.053	1	-0.93
beta_1	0.064	0.068	-0.93	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	10	0.74	0.16	0.733	0.235	0.0934
0.09	10	0.68	0.22	0.693	0.186	-0.216
0.18	10	0.67	0.19	0.652	0.145	0.387
0.27	10	0.59	0.13	0.612	0.111	-0.623
0.36	10	0.58	0.06	0.571	0.0835	0.322

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

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

Model A3: Yij = Mu(i) + e(ij)

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Var{e(ij)} = alpha*(Mu(i))^rho

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

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	68.760362	6	-125.520725
A2	76.244732	10	-132.489465
A3	74.537476	7	-135.074952
fitted	72.450460	4	-136.900920
R	64.715236	2	-125.430471

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	23.059	8	0.003289
Test 2	14.9687	4	0.004766
Test 3	3.41451	3	0.332
Test 4	4.17403	3	0.2433

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

The p-value for Test 2 is less than .05. A non-homogeneous variance model appears to be appropriate

The p-value for Test 3 is greater than .05. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .05. The model chosen seems to adequately describe the data

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 Benchmark Dose Computation
Specified effect =           0.2

Risk Type        =     Relative risk

Confidence level =          0.95

             BMD =      0.326659

            BMDL =        0.2238
```

The $BMDL_{20}$ of 0.2238 mg/kg/day was divided by a total uncertainty factor (UF) of 100 (10 for extrapolation from animals to humans and 10 for human variability) as follows:

Intermediate-duration oral MRL = $BMDL_{20}$ ÷ UF = 0.2238 mg/kg/day ÷ 100 = 0.002 mg/kg/day

Dose end point used for MRL derivation: $BMDL_{20}$ of 0.2238 mg/kg/day for RBC AChE activity

[ ] NOAEL [ ] LOAEL [X] Benchmark

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated from reported mean values for initial body weight, food consumption, and body weight gain for the 42-day treatment period.

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

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

Other additional studies or pertinent information that lend support to this MRL: The selection of the BMD_{20} of 0.3267 mg/kg/day and its lower 95% confidence limit ($BMDL_{20}$) of 0.2238 mg/kg/day from the female rats of the principal study (Davies and Holub 1980a) as a point of departure for deriving an intermediate-duration oral MRL for diazinon is supported by the results of several studies (see Table A-4). These studies collectively indicate that the threshold for less serious AChE inhibition occurs in rats and dogs at repeated oral dose levels between 0.2 and 2 mg/kg/day. The derived intermediate-duration oral MRL of 0.002 mg/kg/day is supported by the free-standing NOAEL of 0.03 mg/kg/day identified in four male volunteers administered diazinon in gelatin capsules at a dose level of 0.03 mg/kg/day for 28–31 days.

Table A-4. NOAELs and LOAELs for RBC and Brain AChE Inhibition Following Intermediate-duration Dietary Exposure to Diazinon

Study type estimated doses (mg/kg/day)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day) AChE inhibition	Reference
28-Day rat study	0.02 (M, F)	2.4; M, F: 38–59% RBC	EPA 1996
M, F: 0, 0.02, 2.4, 23, 213			
30-Day rat study	ND	2.86; 58% RBC	Davies and Holub 1980b
F: 0, 2.86			
35-Day rat study	0.2	ND	Davies and Holub 1980a
F: 0, 0.009, 0.05, 0.09, 0.2			
42-Day rat study	0.2	0.3; 20% RBC	Davies and Holub 1980a
F: 0, 0.09, 0.18, 0.27, 0.36			
6-Week rat study	0.2 (M, F)	2.0; M, F: 46–61% RBC	EPA 2000a
0, 0.02, 0.05, 0.2, 2, 9.5, 28			
6-Week rat study			EPA 2000a
M: 0, 0.02, 0.04, 0.17, 1.68, 8.6, 25.8	0.17 (M)	1.68; M: 29–35% RBC	
F: 0, 0.02, 0.05, 0.19, 1.82, 9.27, 29	0.19 (F)	1.82; F: 16–35% RBC	
6-Week rat study	0.2 (M, F)	8.4; M: 21% RBC	Singh 1988
M: 0, 0.04, 0.2, 8.4, 165			
F: 0, 0.05, 0.2, 9.4, 198		9.4; F: 21% RBC and 24% brain	
90-Day rat study			Singh 1988
M: 0, 0.03, 0.3, 15, 168	0.3 (M)	15; M: 27% RBC	
F: 0, 0.04, 0.4, 19, 212	0.4 (F)	19; F: 41% RBC	
90-Day rat study	0.018 (M, F)	1.8; M, F: 37–75% RBC	EPA 1996
0, 0.018, 1.8, 18, 180			
92-Day rat study	0.4	0.7; 40% RBC	Davies and Holub 1980a
F: 0, 0.4, 0.7, 1			
4-Week dog study			Barnes 1988
M: 0, 0.02, 0.073, 0.8, 14.68	0.8 (M)	14.68; M: 25% RBC; 31% brain	
F: 0, 0.023, 0.082, 0.75, 15.99	0.75 (F)	5.6; F: 31% RBC; 30% brain	
13-Week dog study	0.02 (M, F)		Barnes 1988
M: 0, 0.0034, 0.02, 5.9, 10.9		5.9; M: 26% RBC; 31% brain	
F: 0, 0.0037, 0.02, 5.6, 11.6		5.6; F: 31% RBC ; 30% brain	

AChE = acetylcholinesterase; F = female; LOAEL = lowest-observed-adverse-effect level; M = male; ND = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Diazinon
CAS Numbers: 333-41-5
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 91
Species: Rat

Minimal Risk Level: 0.0007 [X] mg/kg/day [ ] mg/m^3

Reference: Kirchner FR, McCormick GC, Arthur AT. 1991. One/two year oral toxicity study in rats. Ciba-Geigy Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41942002.

Experimental design: (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Diazinon MG-8 (purity 87.7%) was dissolved in acetone vehicle and added to the diet of male and female Sprague-Dawley rats at concentrations of 0, 0.1, 1.5, 125, or 250 ppm for up to 98 weeks. The study included both untreated and vehicle control groups. According to the study report, the corresponding doses were 0, 0.004, 0.06, 5, and 10 mg/kg/day for males and 0, 0.005, 0.07, 6, and 12 mg/kg/day for females). Averaged among male and female rats, the corresponding doses were 0, 0.0045, 0.065, 5.5, and 11 mg/kg/day. Twenty rats/sex/group were treated for the full 98 weeks. Ten rats/sex/group were treated for 52 weeks and sacrificed for interim assessment. Additional groups of 10 rats/sex were assigned to the untreated control, vehicle control, and 250 ppm groups and assessed for recovery 45 days following 52 weeks of treatment. Animals were observed daily for clinical signs of toxicity. Food consumption, water intake, and body weights were monitored. Ophthalmoscopic examinations were performed during weeks 2, 51, and 97 or 98. Blood was collected at several timepoints between days 88 and 684. Ten animals/sex/group from the 98-week treatment groups received clinical chemistry evaluation at treatment days 88, 181, 356, 390, 552, and 684. Urinalysis was performed on all surviving rats of the 98-week treatment groups at treatment days 81, 189, 350, 545, and 679. All rats were subjected to comprehensive gross and microscopic pathologic examination at death or sacrifice.

Effect noted in study and corresponding doses: There were no apparent treatment-related effects on survival, food or water consumption, body weights, or hematological or urinalysis parameters examined. Due to mortality in all groups including controls the study was terminated at 97 weeks. Ophthalmoscopic and gross and microscopic examinations did not reveal evidence of dose-related effects. The major findings of this study were those of dose-related decreased plasma ChE and RBC and brain AChE activity in both male and female rats. Significantly decreased plasma ChE activity (28–51% lower than controls) was noted in 0.065 mg/kg/day male rats at treatment days 88 and 684, but not at treatment days 181, 356, or 552 and in 0.065 mg/kg/day female rats (approximately 50% lower than controls) at most timepoints. High-dose male and female rats consistently exhibited significantly decreased plasma ChE activity, ranging from 80 to 97% lower than controls. In 0.065 mg/kg/day groups, RBC and brain AChE activity was not significantly decreased at any timepoint. The 5.5 mg/kg/day groups exhibited significantly decreased RBC AChE activity at all timepoints, ranging in magnitude from 15 to 28% and from 22 to 25% in males and females, respectively. At the 5.5 and 11 mg/kg/day levels, the magnitude of the effect did not appear to increase with either duration of treatment or increased dose. Following 52 weeks of treatment and 45 days of recovery, RBC AChE activity had returned to control levels in high-dose male rats and to within 7% of control levels in high-dose female rats. Brain AChE activity was significantly decreased in 5.5 and 11 mg/kg/day male and female rats. In 5.5 and 11 mg/kg/day males, the magnitude

of the effect was effect was 24 and 42%, respectively, after 684 days of treatment, but not significantly different from controls at 370 days. In 5.5 and 11 mg/kg/day female rats, the effect was noted at both 370- and 684-day timepoints; the magnitude of the effect was >24% at 5.5 mg/kg/day and >40% at 11 mg/kg/day. This study identified a NOAEL of 0.065 mg/kg/day (1.5 ppm of diazinon in the diet) and a LOAEL of 5.5 mg/kg/day (125 ppm of diazinon in the diet) for 22–28% decreased RBC AChE activity in male and female rats administered diazinon in the diet for up to 97 weeks, which is considered the critical effect. The effect was observed as early as day 88 of treatment and did not appear to increase in magnitude with duration of treatment.

Dose and end point used for MRL derivation: A NOAEL of 0.065 mg/kg/day; the LOAEL was 5.5 mg/kg/day for 22–28% decreased RBC AChE activity

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Estimated doses were included in the original study.

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

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

Other additional studies or pertinent information that lend support to this MRL: Groups of 5-month-old male and female Beagle dogs (4/sex/group) were administered diazinon MG-8 (87.7% purity) in the diet for 52 weeks at concentrations of 0, 0.1, 0.5, 150, or 300 ppm (Rudzki et al. 1991). The highest dose level was reduced to 225 ppm after 14 weeks due to the lack of body weight gain at the 300 ppm level. According to the study authors, the corresponding diazinon doses (adjusted for purity) were 0, 0.0032, 0.015, 4.7, and 7.7 mg/kg/day for the males and 0, 0.0037, 0.02, 4.5, and 9.1 mg/kg/day for the females. Averaged among male and female dogs, the corresponding doses were 0, 0.0034, 0.017, 4.6, and 7.9 mg/kg/day. Animals were observed daily for clinical signs of toxicity. Food consumption and body weights were monitored throughout the study. Physical, auditory, and ophthalmoscopic examinations were periodically performed. Blood and urine were collected 4 weeks prior to dosing and during treatment weeks 13, 26, 39, and 52 for hematological and clinical chemistry assessment and urinalysis. At death or scheduled sacrifice, organ weights were recorded and all animals were subjected to histological examination of all major organs and tissues. One high-dose male was sacrificed on test day 2 and one female in the 0.5 ppm group was found dead on test day 12. Both deaths were attributed to gastrointestinal infections and the animals were replaced. Clinical signs of toxicity were limited to a single high-dose male that exhibited signs of dehydration and emaciation. Although food consumption in all treatment groups of male and female dogs was lower than that of controls at most timepoints during the 52 weeks of treatment, there was no clear pattern of dose-related decreased food consumption. The 4.6 mg/kg/day dose level may represent a LOAEL for body weight gain in the males, but a clear effect level for body weight gain was not identified in females. Plasma ChE inhibition generally exceeded 20% in all dose groups of males and females, with the exception of the 0.0034 mg/kg/day groups. Significant RBC AChE inhibition (magnitude ranging from approximately 21 to 35%) was noted in treated males and females of the two highest exposure groups (4.6 and 7.9 mg/kg/day), but not at lower exposure levels.

Significant brain AChE inhibition was noted at 4.6 and 7.9 mg/kg/day in females (magnitude 25.5 and 34.7%, respectively). High-dose males exhibited 24.8% brain AChE inhibition (not statistically significant). Although serum amylase activity was generally increased in diazinon-treated male and female dogs at most timepoints, the only statistically significant increase occurred in 4.6 mg/kg/day males only at week 52. There were no other treatment-related effects on clinical chemistry parameters examined. Ophthalmoscopic examinations, hematology, and urinalysis did not reveal evidence of treatment-related effects. There were no apparent treatment-related effects on organ weights and extensive gross and microscopic examinations were unremarkable. This study identified a NOAEL of 0.5 ppm (0.017 mg/kg/day) and a LOAEL of 150 ppm (4.6 mg/kg/day) for RBC AChE inhibition of 20% or more in both male and female dogs.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.; Carolyn Harper, Ph.D.; Paula Burgess, M.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

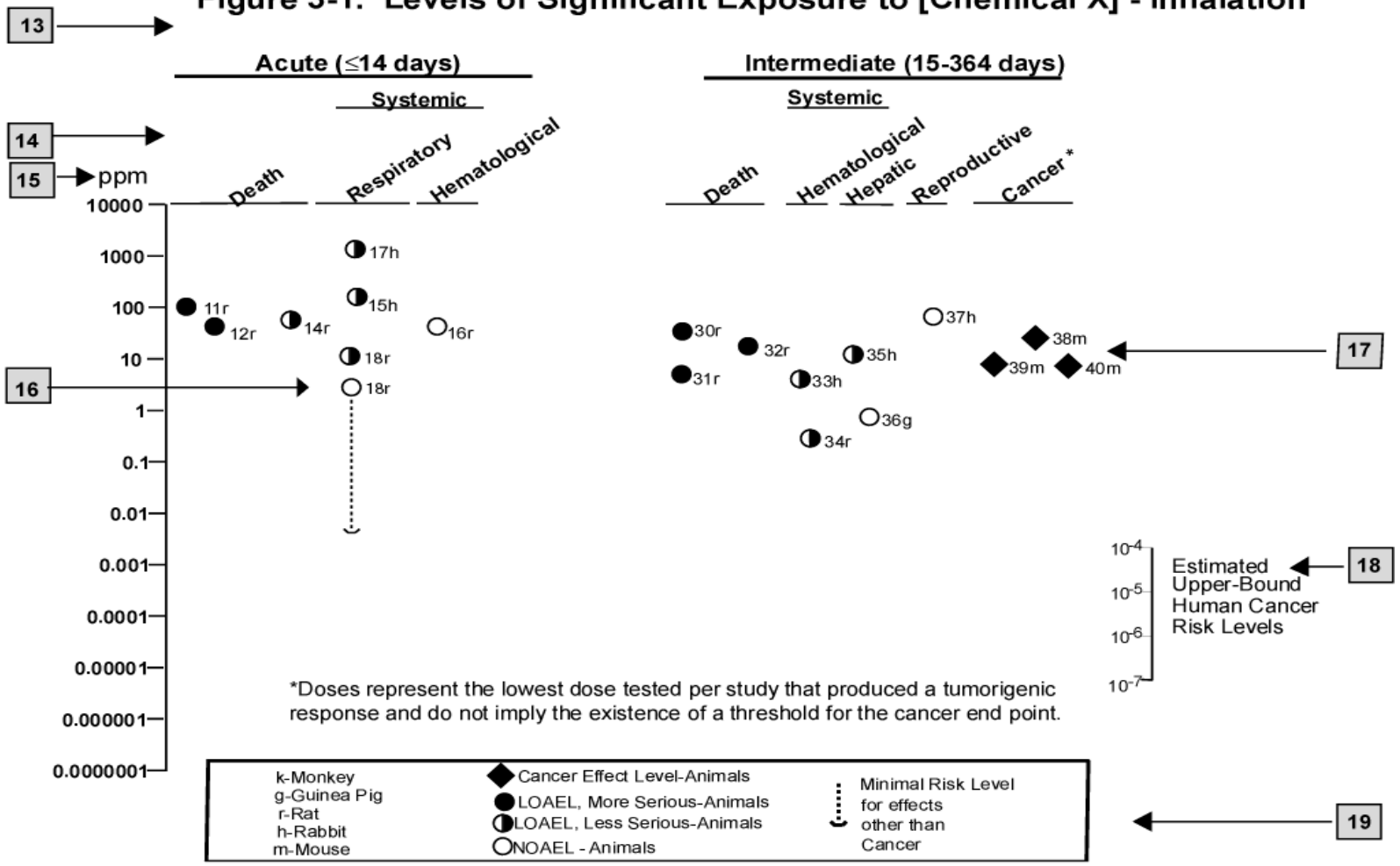
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX

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