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 route and 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 substance-induced endpoint 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 Human Health Sciences, 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 Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene diisocyanate
CAS Number: 26471-62-5
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 1
Species: Humans

Minimal Risk Level: $1x10^{-5}$ [ ] mg/kg/day [X] ppm

Reference: Vandenplas O, Delwiche J-P, Staquet P, et al. 1999. Pulmonary effects of short-term exposure to low levels of toluene diisocyanate in asymptomatic subjects. Eur Respir J 13:1144-1150.

Experimental design: In this single-blind crossover design study, 17 volunteers (8 male, 9 females) were exposed to ambient air or 0.005 ppm TDI for 6 hours followed by a 20-minute exposure to 0.020 ppm TDI. Pulmonary function testing was conducted prior to exposure and every hour during the 6-hour exposure and at the end of the 20-minute exposure to 0.020 ppm or air. Bronchial lavage (BL) and bronchoalveolar lavage (BAL) were performed 1 hour after the end of the exposure.

Effect noted in study and corresponding doses: None of the subjects reported respiratory symptoms in response to the exposure. TDI exposure was associated with a slight, but significant, decrease in specific airway conductance (sGaw) and maximal expiratory flow at 25% of forced vital capacity ($MEF_{25\%}$). No significant alterations in the volume of fluid recovered or total and differential cell counts were observed in the BL and BAL after TDI exposure, as compared to air exposure. Exposure to TDI was associated with a decrease in the proportion of CD19 cells in the BL and BAL, although there was no difference in the absolute number of cells. A slight but statistically significant increase in BAL albumin levels and BL α-2-macroglobulin levels were observed.

Dose and end point used for MRL derivation: LOAEL of 0.005 ppm for decreased lung function

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

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? Yes. The LOAEL of 0.005 ppm was adjusted for intermittent exposure:

0.005 ppm x 6 hours/24 hours = 0.00125 ppm

Other additional studies or pertinent information that lend support to this MRL: In another acute-duration human study, no alterations in specific air way resistance were observed in healthy or asthmatic subjects exposed to 0.02 ppm TDI for 20 minutes (Chester et al. 1979). Acute-duration animal inhalation studies have reported rhinitis, lung damage, and airway hyperresponsiveness. The severity of rhinitis was concentration-related; moderate rhinitis was observed in mice exposed to 0.07 ppm 6 hours/day for 4 days (Zissu 1995), moderate-to-severe rhinitis was observed in mice exposed to 0.4 ppm 6 hours/day for 5 days (Buckley et al. 1984), and severe nasal lesions were observed in mice exposed to 1 ppm 6 hours/day for 3 days (Arts et al. 2008). Interstitial inflammation, pleural thickening, and goblet cell hyperplasia were observed in the lungs of guinea pigs exposed to 1.4 ppm TDI 3 hours/day for 3 days (Wong et al. 1985). Airway hyperresponsiveness to methacholine or acetylcholine was also observed in guinea pigs and mice exposed to ≥0.01 ppm (Gagnaire et al. 1996; Gordon et al. 1985; Marek et al. 1999); a NOAEL of 0.005 ppm for airway hyperresponsiveness was identified in guinea pigs exposed to TDI 6 hours/day for 5 days (Marek et al. 1999). An increase in the incidence of litters with poorly ossified cervical centrum was observed in the offspring of rats exposed to 0.5 ppm commercial-grade TDI 6 hours/day on GDs 6–15 (Tyl et al. 1999a); this concentration was also associated with maternal toxicity including a marked decrease in body weight gain and signs of nasal irritation and audible respiration.

Support for basing the MRL on a single exposure study comes from chronic occupational exposure studies. The lowest LOAEL values identified in longitudinal studies of workers exposed to TDI were 0.0012 and 0.0019 ppm (Clark et al. 1998; Diem et al. 1982); the effects observed at these concentrations included decreases in lung function (FEV_1 and/or FVC). These LOAELs are roughly 2–4 times lower than the LOAEL from the Vandenplas et al. (1999) study. However, since there is uncertainty that the MRL would be protective for continuous exposure for 14 days, it is suggested that measured air concentrations should not exceed the MRL of $1x10^{-5}$ ppm during a 24-hour period.

Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Toluene diisocyanate
CAS Number: 26471-62-5
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 26
Species: Humans

Minimal Risk Level: $3x10^{-6}$ [ ] mg/kg/day [X] ppm

Reference: Clark RL, Bugler J, McDermott M, et al. 1998. An epidemiology study of lung function changes of toluene diisocyanate foam workers in the United Kingdom. Int Arch Occup Environ Health 71:169-179.

Experimental design: A group of 780 (649 males, 131 females) workers employed at 12 flexible foam-producing factories in the United Kingdom were examined over a 5-year period; all subjects had taken at least three pulmonary function tests over a period of at least 1 year. Workers were divided into three groups: (1) the exposed group (472 males and 49 females), which consisted of workers employed in the manufacture of polyurethane foam or were handling freshly manufactured products still emitting measurable quantities of TDI; (2) the handling group (80 males and 43 females), consisting of workers handling cold polyurethane products from which TDI emissions could not usually be detected; and (3) the low-exposure group (97 males and 39 females), consisting of shop floor and office workers (control group). The average time in the study was 4.3 years. Workers completed respiratory questionnaires at the start of the study and at the end (or when they left the study); pulmonary function testing was conducted annually at the same time of day, same day of the week, and same month of the year. The mean daily exposure to TDI was 0.0096-hours ppm (0.0012 ppm 8-hour TWA). The investigators noted that although 4.7% of the measurements exceeded the 8-hour TWA concentration limit of 0.0058 ppm, most of the subjects were exposed to <0.00125 ppm. Additionally, 19% of the samples in the exposed group exceeded the 15-minute short-term limit of 0.02 ppm.

Effect noted in study and corresponding doses: Significant increases in the prevalence of wheezing were observed in the handling and exposed groups; however, there were only small differences between the two groups. Longitudinal analysis did not find a significant exposure-related effect on lung function. Twenty-four cases of respiratory sensitization were identified; the FEV_1 decline was greater in these subjects than those not sensitized. A study of 157 naïve subjects (workers who entered the study after the first longitudinal measurements were made) showed no difference in FEV_1 decline as compared to exposed non-naïves. However, longitudinal regression showed the mean daily exposure to be significant for annual changes in FEV_1 and FVC. These declines were more rapid in the early years of employment, frequently during the first few months of employment. Clark et al. (1998) suggested that the decline in lung function may have been due to respiratory irritation.

Dose and end point used for MRL derivation: The MRL was based on the mean daily exposure level for the exposed group of 0.0012 ppm that was associated with a significant decrease in lung function; this concentration was treated as an adverse effect level for the purposes of deriving the MRL.

[ ] NOAEL [X] Adverse Effect Level (AEL)

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a AEL
[ ] 10 for extrapolation from animals to humans
[X] 10 for human variability

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

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? Yes. The AEL of 0.0012 ppm was adjusted for intermittent exposure:

0.0012 ppm x 8 hours/24 hours x 5 days/7 days = 0.00029 ppm

Other additional studies or pertinent information that lend support to this MRL: The toxicity of TDI has been examined in a large number of occupational exposure studies that identify the respiratory tract as the primary target of toxicity; they are supported by a number of animal studies. In humans, the primary respiratory effects are occupational asthma, asthma-like symptoms (e.g., wheezing, dyspnea, chest tightness), and decreases in lung function. The occupational asthma and possibly the asthma-like symptoms are observed in individuals sensitized to TDI. Although the prevalence of sensitization is not known, it is likely <10% based on older literature when the occupational exposures were higher and may now be as low as <1% since the occupational exposure limit was lowered to 0.005 ppm (Ott et al. 2003). Exposure to very low concentrations of TDI can elicit an asthma response in sensitized individuals; in non-sensitized individuals, this concentration would be non-irritating. Although there is some indication of an improvement in asthma symptoms after discontinuing TDI exposure, a fair percentage of sensitized workers still report symptoms >10 years after exposure termination (Mapp et al. 1988; Moller et al. 1986; Moscato et al. 1991; Padoan et al. 2003; Paggiaro et al. 1984).

The primary effect observed in non-sensitized workers is a decline in lung function (Adams 1975; Bodner et al. 2001; Butcher et al. 1977; Clark et al. 1998, 2003; Diem et al. 1982; Jones et al. 1992; Omae et al. 1992; Ott et al. 2000; Peters et al. 1970; Wegman et al. 1977, 1982). Based on the results of the Clark et al. (1998) study and a prospective longitudinal study by Diem et al. (1982), it appears that the greatest declines in lung function occur during the first couple of years of exposure to TDI; thereafter, continued exposure to lower TDI levels does not result in further annual declines in lung function.

Chronic exposure to TDI resulted in chronic or necrotic rhinitis with epithelial atrophy and mucous and squamous metaplasia in mice exposed to 0.05 ppm TDI 6 hours/day, 5 days/week for 2 years (Loeser 1983). In the lungs, interstitial pneumonitis and catarrhal bronchitis were observed.

Agency Contact (Chemical Manager): Malcolm Williams

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Polymeric methylenediphenyl diisocyanate
CAS Number: 9016-87-9
Date: June 2018
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 8
Species: Rat

Minimal Risk Level: 0.001 [ ] mg/kg/day [X] mg/m^3

Reference: Reuzel PGJ, Arts JHE, Lomax LG, et al. 1994. Chronic inhalation toxicity and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam Appl Toxicol 22:195-210.

Experimental design: Groups of 70 male and 70 female Wistar rats were exposed to 0, 0.2, 1.0, or 6.0 mg/m^3 polymeric MDI for 6 hours/day, 5 days/week for 2 years; after 1 year of exposure, 10 rats/sex/group were sacrificed for interim evaluation. The test substance contained 44.8–50.2% monomeric MDI. The mass median aerodynamic diameter (MMAD) particle sizes (and geometric standard deviation [GSD]) were 0.68 (2.93), 0.70 (2.46), and 0.74 (2.31) µm, respectively. The following parameters were used to evaluate toxicity in the rats exposed for 1 year: clinical signs, body weight (weekly for the first 13 weeks and monthly thereafter), hematology (red and white blood cell counts, hemoglobin, packed cell volume, differential white blood cell count, prothrombin time), urinary parameters (volume, density, pH, protein, occult blood, glucose, ketones), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea nitrogen, total protein, creatinine, electrolytes, inorganic phosphate, cholesterol, triglycerides and glucose), and histopathological examination of major tissues and organs. Histopathological examination of major tissues and organs was also conducted in the control and 6.0 mg/m^3 after 2 years of exposure and the nose, lungs, and mediastinal lymph nodes were examined in the 0.2 and 1.0 mg/m^3 group after 2 years of exposure.

Effect noted in study and corresponding doses: Sniffing (no additional information provided) was observed in the 6.0 mg/m^3 group after removal from the exposure chamber during months 5 and 6. No treatment-related increases in mortality were observed, and there were no alterations in body weight gain. No alterations in hematological, clinical chemistry, or urinalysis parameters were observed. Significant increases in absolute and relative lung weights were observed in the 6.0 mg/m^3 group after 1 and 2 years of exposure. In the rats sacrificed after 1 year of exposure, histological alterations were observed in the nasal cavity, lungs, and mediastinal lymph nodes. In the lungs, the lesions consisted of pneumonitis in the 1.0 and 6.0 mg/m^3 males, alveolar duct epithelialization in males at 6.0 mg/m^3 and females at 1.0 and 6.0 mg/m^3, and minimal to moderate localized fibrosis and accumulation of macrophages with yellow pigment in the 6.0 mg/m^3 males and females. An accumulation of macrophages with yellow pigment was also observed in the lymph nodes of male and female rats exposed to 1.0 or 6.0 mg/m^3. In the nasal cavity, minimal to moderate olfactory epithelial disarrangement was observed in males at 6.0 mg/m^3. Alterations were also observed in the lungs, mediastinal lymph nodes, and nasal cavity after 2 years of exposure. Lung effects included adenoma in males exposed to 6.0 mg/m^3, accumulation of macrophages with yellow pigment in males and females at 1.0 and 6.0 mg/m^3, localized fibrosis in males at 1.0 and 6.0 mg/m^3 and females at 6.0 mg/m^3, alveolar duct epithelialization in males and females at 1.0 and 6.0 mg/^{3}, and localized alveolar bronchiolization in males and females at 6.0 mg/m^3. An accumulation of macrophages with yellow pigment was observed in the mediastinal lymph nodes in males at 1.0 and 6.0 mg/m^3 and females at 6.0 mg/m^3. Nasal effects included basal cell hyperplasia and Bowman's gland

hyperplasia in males at 1.0 and 6.0 mg/m^3, basal cell hyperplasia in females at 6.0 mg/m^3, and minimal to severe olfactory epithelial degeneration in males and females at 6.0 mg/m^3. No significant increases in tumors were observed.

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.48 mg/m^{3}for basal cell hyperplasia

[ ] NOAEL [ ] LOAEL [X] BMCL

The incidence data (Table A-1) for basal cell hyperplasia in the nasal cavity, Bowman's duct hyperplasia in the nasal cavity, and lung fibrosis were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark dose response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the point of departure when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all three lesion types, a BMR of 10% was used. The model predictions for basal cell hyperplasia are presented in Table A-2. The incidence data for Bowman's gland hyperplasia did not fit any of the available dichotomous models. The model predictions for the incidence of lung fibrosis are presented in Table A-3.

Table A-1. Incidence of Nasal and Pulmonary Lesions in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate

	Exposure concentration (mg/m^3)			
	0	0.2	1.0	6.0
Basal cell hyperplasia	14/60	13/60	26/60	32/60
Bowman's gland hyperplasia	0/60	2/60	9/60	17/60
Lung fibrosis	1/60	0/60	9/60	44/60

Source: Reuzel et al. 1994

Table A-2. Model Predictions for Incidence of Basal Cell Hyperplasia in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Logistic	2	5.76	0.06	2.01	-0.28	2.01	302.55	ND	ND
LogLogistic[d,f]	**2**	**3.96**	**0.14**	**1.67**	**-0.62**	**1.67**	**300.81**	**0.87**	**0.48**
LogProbit[d]	2	7.56	0.02	2.30	-0.28	2.30	304.25	ND	ND
Multistage (1 degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Multistage (2 degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Multistage (3-degree)[e]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Probit	2	5.7	0.06	2.00	-0.29	2.00	302.49	ND	ND
Weibull[c]	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND
Quantal-Linear	2	4.8	0.09	1.87	-0.45	1.87	301.60	ND	ND

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, model does not provide adequate fit to the data

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. The only model that was fit to the data was the LogLogistic model (all other models had a p-value <0.1).

Table A-3. Model Predictions for Incidence of Lung Fibrosis in Male Rats Exposed to Methylenediphenyl Diisocyanate (mg/m^3)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	1	2.04	0.15	0.63	-0.16	-1.12	139.67	0.90	0.57
Logistic	2	8.46	0.01	2.23	-0.20	2.23	144.69	ND	ND
LogLogistic[d,f]	1	1.73	0.19	0.43	-0.15	-1.06	139.22	0.87	0.57
LogProbit[d]	**2**	**1.3**	**0.52**	**0.35**	**-0.20**	**-0.84**	**136.40**	**0.87**	**0.70**
Multistage (1-degree)[e]	2	4.42	0.11	-0.65	0.73	-1.69	141.53	0.54	0.43
Multistage (2-degree)[e]	1	2.64	0.10	0.67	-0.07	-1.36	140.83	0.89	0.51
Multistage (3-degree)[e]	1	2.64	0.10	0.67	-0.07	-1.36	140.83	0.89	0.51
Probit	2	7.46	0.02	2.11	-0.23	2.11	143.53	ND	ND
Weibull[c]	1	2.2	0.14	0.64	-0.12	-1.19	139.99	0.90	0.55
Quantal-Linear	2	4.42	0.11	-0.65	0.73	-1.69	141.53	0.54	0.43

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, model does not provide adequate fit to the data

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models, except for the Logistic and the Probit (p<0.1) were fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (LogLogistic Model).

The $BMCL_{10}$ values predicted from the selected models for basal cell hyperplasia and lung fibrosis were 0.48 and 0.70 mg/m^3; the LogLogistic and LogProbit models for these effects are presented in Figures A-1 and A-2. The $BMCL_{10}$ of 0.48 mg/m^3 was selected as the point of departure for the MRL.

Figure A-1. Fit of LogLogistic Model to Data on Incidence of Basal Cell Hyperplasia in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)

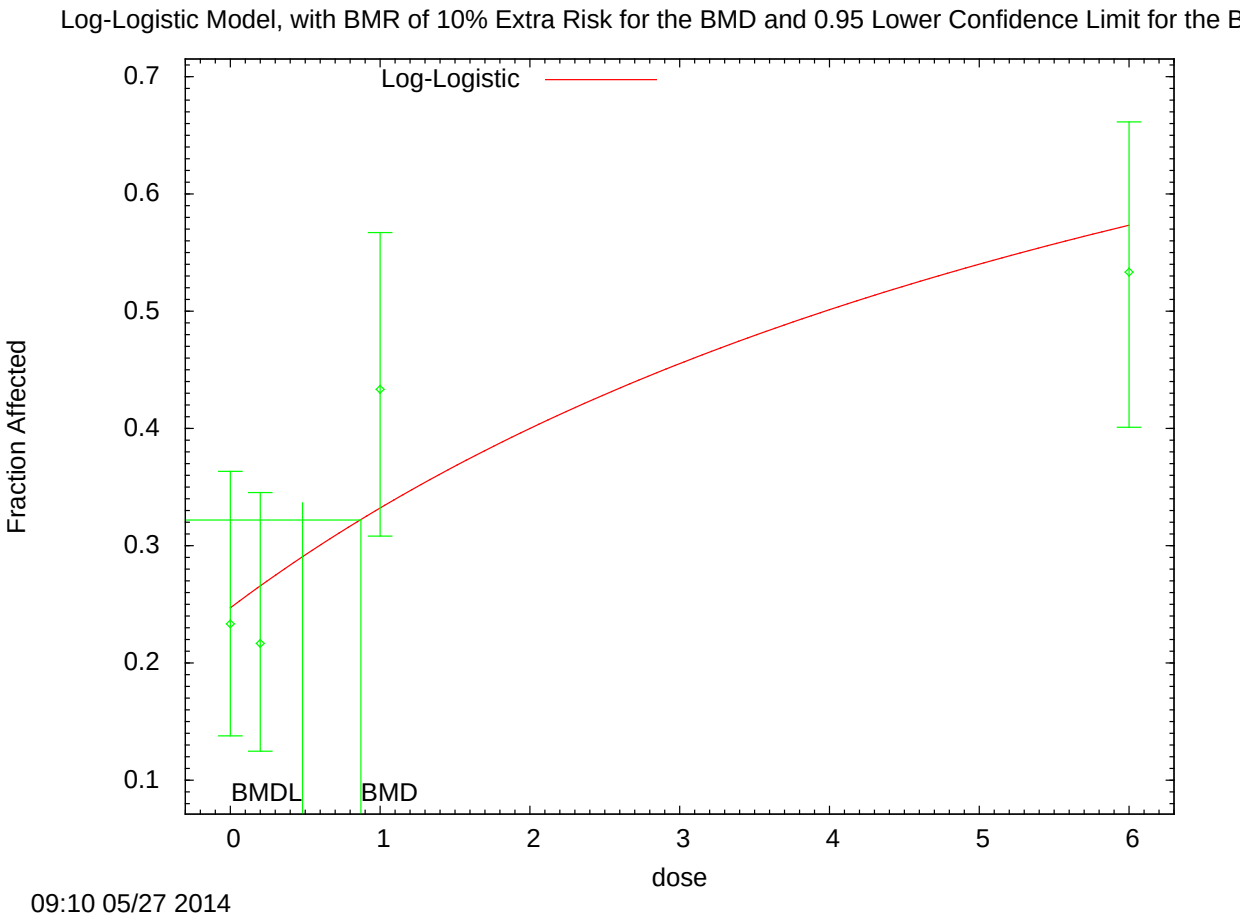
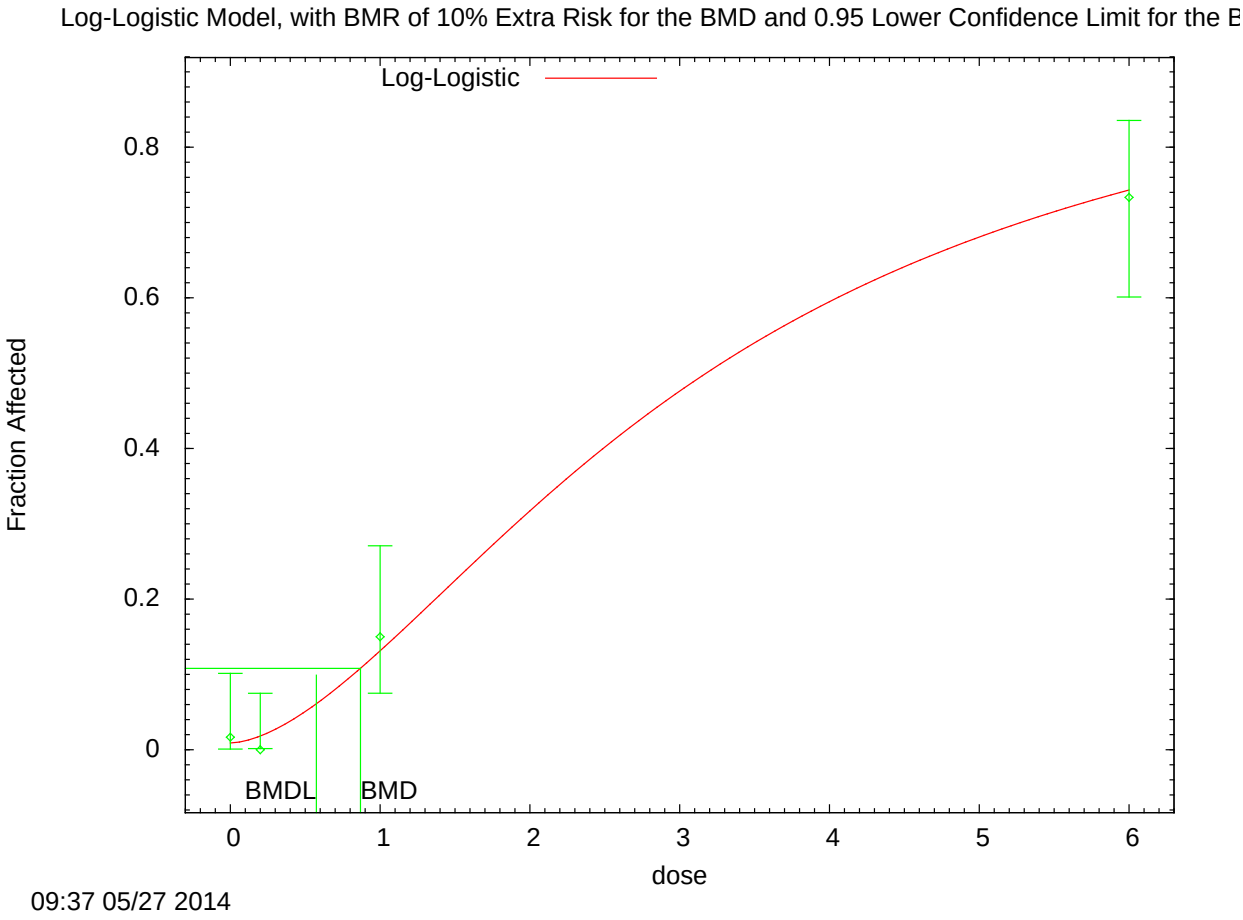


Figure A-2. Fit of LogLogistic Model to Data on for Incidence of Lung Fibrosis in Male Rats Exposed to Polymeric Methylenediphenyl Diisocyanate (mg/m^3)



Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

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

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

The $BMCL_{ADJ}$ of 0.086 mg/m^3 was converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.039 mg/m^3 using the RDDR program (EPA 1990) as follows:

$BMCL_{HEC} = BMCL_{ADJ}$ x RDDR
$BMCL_{HEC}$ = 0.086 mg /m^3 x 0.453
$BMCL_{HEC}$ = 0.039 mg/m^3

where:

RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal to the predicted inhalation particulate exposure concentration for a human. The RDDR multiplier of 0.453 for the extrathoracic region tract was determined using the default chronic body weight of 462 g for male Wistar rats (EPA 1988) and a particle size MMAD±GSD of 0.68±2.93 µm reported in the Reuzel et al. (1994) study.

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

A $BMCL_{ADJ}$ was calculated by adjusting the $BMCL_{10}$ of 0.48 mg/m^3 for intermittent exposure:

$$0.048\ mg/m^3 \times 6\ hours/24\ hours \times 5\ days/7\ days = 0.086\ mg/m^3$$

Other additional studies or pertinent information that lend support to this MRL: The respiratory tract is the primary target of MDI toxicity in humans and animals. Occupational asthma, asthma-like symptoms, and decreases in lung function have been reported in occupational exposure studies (Hur et al. 2008; Liss et al. 1988; Musk et al. 1982; Sulotto et al. 1990; Wang and Petsonk 2004; Woellner et al. 1997; Zamit-Tabona et al. 1983). The occupational asthma and asthma-like symptoms result from sensitization to MDI following a brief exposure to very high concentrations or prolonged exposure to lower concentrations; the prevalence of MDI-sensitization is believed to be low. Liss et al. (1988) reported significant declines in FEV_1 levels when pre-shift levels were compared to post-shift levels; however, the study did not provide monitoring data. Sulotto et al. (1990) and Musk et al. (1982) did not find declines in lung function in workers. Sulotto et al. (1990) reported MDI levels ranging from 0.005 to 0.001 ppm; the monitoring data provided by Musk et al. (1982) was not considered reliable.

Agency Contacts (Chemical Managers): Malcolm Williams

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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 hazardous substance 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 include 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 adverse 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 an adverse 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

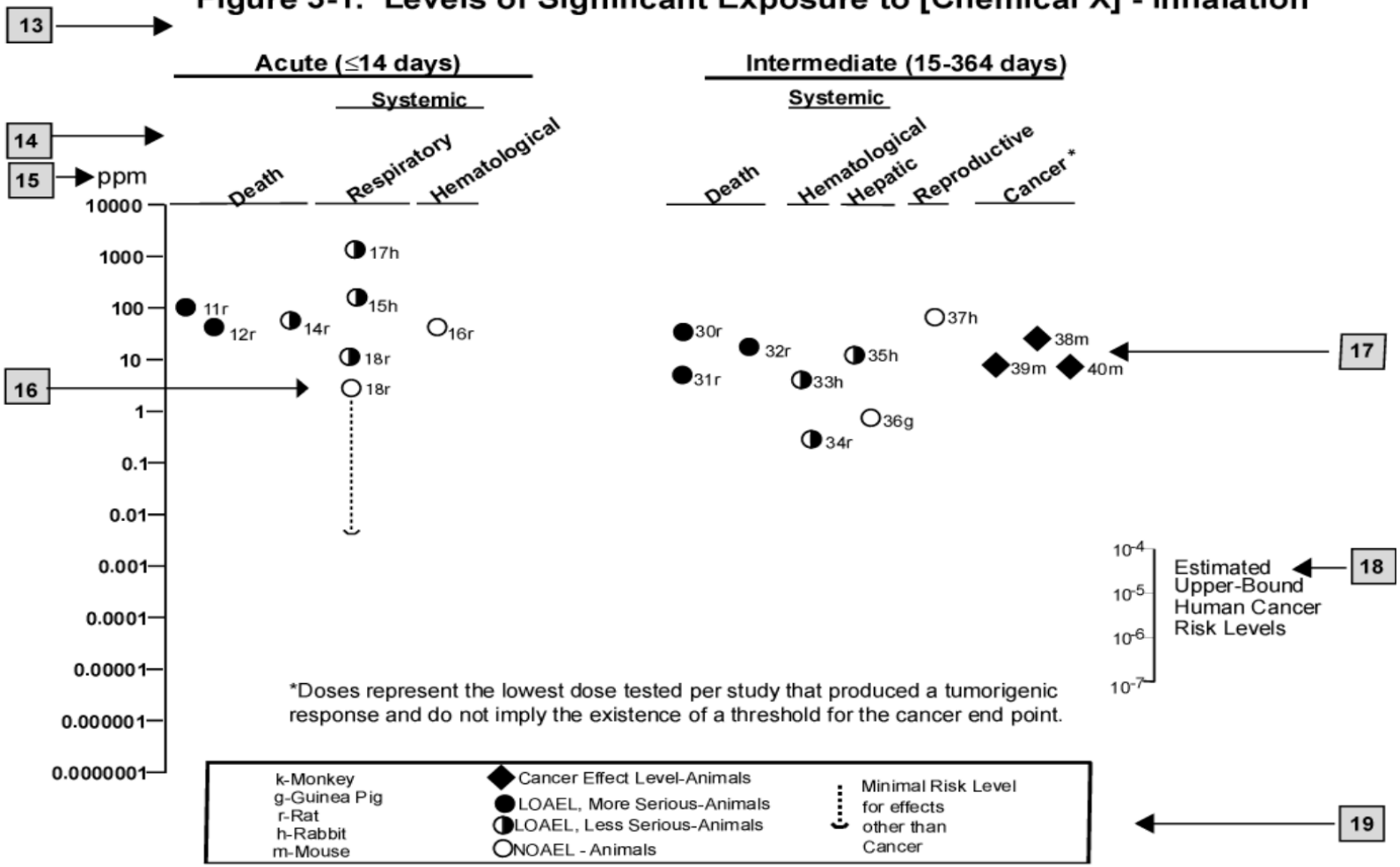
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 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
mt	metric ton
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
PEL-C	permissible exposure limit-ceiling value
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
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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 (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
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
TLV-C	threshold limit value-ceiling 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