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 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.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: June 2015
Profile Status: Final, Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 32
Species: Rabbit

Minimal Risk Level: 0.007 [X] mg/kg/day [ ] ppm

Reference: MacKenzie KM, Felton SM, Dickie SM, et al. 1981. Raltech Study No. 80070. Teratology study with FMC 5462 in rabbits. FMC Corporation. Submitted to U.S. Environmental Protection Agency. MRID504800201.

Experimental design: Groups of mated New Zealand White rabbits (20/ dose group) were administered technical endosulfan by gavage in corn oil in doses of 0, 0.3, 0.7, or 1.8 mg/kg/day from GD 6 to 28; dams were sacrificed on GD 29. Body weight was measured on GD 0 and 6 and at 6-day intervals thereafter. Body weight was also measured on sacrifice day (actual and corrected for gravid uterine weight). Clinical signs were monitored twice daily. At necropsy, the ovaries were removed and examined for gross abnormalities and the number of corpora lutea was recorded. The gravid uterus was weighed and opened after external examination. The following parameters were recorded: number and location of live and dead fetuses, early and late resorptions, empty sites and implantation scars, unusual coloration and variation in amniotic fluid and placenta, and any other abnormalities. Fetuses, were sexed, measured, weighed, examined grossly, and given a thorough visceral examination and then prepared for skeletal examination.

Effect noted in study and corresponding doses: Since deaths occurred in the high-dose group (not totally clear when these deaths occurred), 6 mated females were added to this group for a total of 26 dams. It appears that after the six dams were added to the high-dose group, four dams died before the study termination, three of them possibly due to regurgitation and aspiration of the test material into the trachea and lung and the fourth of unestablished causes. No deaths occurred in the other groups. Neurological signs were observed in three high-dose dams within 4 days of the start of treatment (in one female on GD 6, the day of the first dose, and in two females on GD 10, after four doses). The signs consisted of noisy and rapid breathing, hyperactivity and convulsions. No such signs occurred in the other treated groups or in the control group. No rabbits aborted during this study. Treatment with endosulfan did not significantly affect body weight changes between GD 0 and 29 (corrected or uncorrected). Exposure to endosulfan did not significantly alter pregnancy maintenance, implantation, litter size, sex ratio, mean fetal weight and length, or number and percent of live or resorbed fetuses. There were no dead fetuses in any treatment group or in controls. Exposure to endosulfan also did not result in dose-related increased incidences of gross, soft tissue, or skeletal malformations.

As indicated in Section 2.3, although the incidence of neurological effects of 3/26 reported in the high-dose group within 4 days after dosing started is not statistically different from 0/20 in the other groups ($p=0.1713$, Fisher Exact Test), it is appropriate to consider the 1.8 mg/kg/day dose level a LOAEL based on the biological significance of the effect. Therefore, the dose level of 1.8 mg/kg/day in the MacKenzie et al. (1981) study is considered an acute LOAEL for neurological signs; the NOAEL is 0.7 mg/kg/day.

Incidence data for neurological signs in rabbits occurring within 14 days after dosing started in the MacKenzie et al. (1981) study were analyzed using the BMD approach. The incidence data were 0/20, 0/20, 0/20, and 3/26 in the control, 0.3, 0.7, and 1.8 mg/kg/day dose groups, respectively. Models in the EPA BMDS (version 2.1.1) were fit to the data set to determine potential PODs for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the POD when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) is chosen. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body weight, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight/gain equal to 1 standard deviation from the control mean (EPA 2000a). Using the criteria for model selection mentioned above, the Gamma model (BMD_{10} 1.76 mg/kg/day; $BMDL_{10}$ 1.23 mg/kg/day) was selected as the best model to fit the incidence of clinical signs in pregnant female rabbits. However, the $BMDL_{10}$ of 1.23 mg/kg/day is not only very close to the BMD_{10} of 1.76 mg/kg/day, a dose that caused serious effects in the study, but it is even closer to a dose of 1.5 mg/kg/day, which caused the same type of serious clinical signs and even death in one of nine rabbits in the Hatipoglu et al. (2008) study. Taking this into consideration and in the interest of protecting human health, the NOAEL of 0.7 mg/kg/day for clinical signs in the MacKenzie et al. (1981) study is preferred as the POD for derivation of an acute-duration oral MRL for endosulfan.

Dose and end point used for MRL derivation: 0.7 mg/kg/day; neurological clinical signs.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Neurological effects are characteristic of endosulfan and other chlorinated pesticides in humans and animals. An additional study in rabbits reported clinical signs including hyperexcitability, dyspnea, hyperpnea, intermittent intervals of tremors and tonic-clonic convulsions, thrashing against the cage walls, depression, and forelimb extension leading to death in 1/9 and 2/9 New Zealand White male rabbits 10–40 minutes following gavage dosing with 1.5 or 3 mg/kg endosulfan, respectively (Hatipoglu et al. 2008).

Agency Contact (Chemical Manager): Jessilynn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: June 2015
Profile Status: Final, Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 73
Species: Rat

Minimal Risk Level: 0.005 [X] mg/kg/day [ ] ppm

Reference: Banerjee BD, Hussain QZ. 1986. Effect of sub-chronic endosulfan exposure on humoral and cell-mediated immune responses in albino rats. Arch Toxicol 59:279-284.

Experimental design: Groups of male Wistar (10–12/group) (85–90 g body weight) received technical-grade endosulfan (α- and β-endosulfan in the ratio of 7:3) in their diets at dietary levels of 0, 5, 10, or 20 ppm (equivalent to 0, 0.45, 0.9, and 1.8 mg/kg/day, using the EPA [1988] food factor for male Wistar rats, subchronic duration). Test diets were prepared by dissolving the endosulfan in groundnut oil and mixing this into standard laboratory diet. Samples analyzed from each batch of diet indicated that the actual levels of endosulfan in the diet were within 10% of the desired levels. Control animals received a diet with an equal amount of groundnut oil mixed in. Rats were randomly allocated to groups and were caged four to a stainless steel, mesh-bottom cage. Food and water were available to these rats on "as needed" basis for between 8 and 22 weeks. At weeks 8, 12, 18, and 22, between 10 and 12 rats were selected from each group and sacrificed. Twenty days before sacrifice, the rats were immunized by injecting 0.2 mL of tetanus toxin mixed with an equal volume of Freund's adjuvant subcutaneously. An additional group of 10–12 rats per dose was sacrificed at the time periods indicated, but these rats were not immunized with the tetanus toxin and adjuvant. At the time of sacrifice, the liver, spleen, and thymus were removed and weighed, blood samples were collected by cardiac puncture, and peritoneal exudate was collected by washing the peritoneal cavity with between 10 and 15 mL of RMPI medium.

The antibody titer to tetanus toxin was estimated using an indirect hemagglutination technique. Briefly, a suspension of sheep red blood cells was treated with tannic acid (1:20,000 dilution) and used for antigen coating. Tetanus toxin was then mixed with the treated sheep red blood cell and antibody titers were determined using the first dilution where no visible agglutination was observed. Serum proteins were determined using zone electrophoresis. Quantitation of serum levels of IgG and IgM was performed using radial immunodiffusion in agarose containing either anti IgG or anti IgM. The leukocyte migration inhibition test was performed using leukocytes isolated from rat blood by sequential centrifugation and washing. Migration from micro capillary tubes was measured using a camera lucida and migration into control medium was compared with migration into medium containing tetanus toxin. The macrophage migration inhibition test was performed using microphages isolated from the peritoneal exudate by sequential centrifugation and washing. Migration was measured as described above for the leukocytes.

Effect noted in study and corresponding doses: No difference between the controls and rats given diets containing 5 ppm endosulfan was observed in any of the parameters measured. Rats consuming diets containing 10 ppm endosulfan and treated with tetanus toxin had significantly decreased serum IgG levels at weeks 12, 18, and 22. These rats also had significantly decreased antibody titer to tetanus toxin at weeks 8, 12, 18, and 22. Leukocyte and macrophage migration was also significantly inhibited at weeks 8, 12, 18, and 22. The magnitude of the differences between the 10 ppm rats and the controls increased at each later time point. These rats also had a significantly increased albumin to globulin ratio

at week 22. Rats consuming diets containing 20 ppm showed all of the same changes as the rats at 10 ppm but to a greater degree. In addition, at weeks 2, 18, and 22, these rats showed a significantly increased albumin to globulin ratio, and at 22 weeks, these rats showed a significant decrease in relative spleen weight. No effect on the relative thymus weight was observed at any dose at any of the times tested.

Data from Banerjee and Hussain (1986) were considered for benchmark modeling analysis. However, only the information regarding serum levels of IgM and IgG, which are presented in a table, could have been subjected to benchmark modeling. Data regarding serum antibody titer to tetanus toxoid as well as leucocyte and macrophage migration inhibition were presented in figures from which only approximate values could be determined. Still, Banerjee and Hussain (1986) indicated in the figures the dose levels at which the responses were significantly different from controls. Therefore, since the lowest dose of 0.45 mg/kg/day (5 ppm in the food) was the NOAEL for serum IgG and IgM levels, antibody titer, and leucocyte and macrophage migration inhibition, the NOAEL/LOAEL approach is preferred for MRL derivation since it includes the three data sets. The study LOAEL was 0.9 mg/kg/day (10 ppm in the food).

Dose and end point used for MRL derivation: 0.45 mg/kg/day; depressed immune response.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, 0.45 mg/kg/day was calculated by multiplying the dietary level of 5 ppm (5 mg endosulfan/kg diet) by the food factor for male Wistar rats in a subchronic study of 0.09 kg diet/kg body weight/day (EPA 1988).

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

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: With the exception of a study by Hoechst (1988c), which reported that doses up to 4.5 mg/kg/day given to Wistar rats 2 days before and 10 days after infection with *Trichinella spiralis* larvae resulted in no effect on the number of worms found in the body at sacrifice, no effect on the thymus or spleen weights, and no effect on the percent lymphocytes or white blood cell count, the study by Banerjee and Hussain (1986) is the only one that has examined immunocompetence in response to an infective agent, and would be helpful to try to replicate it. Vos et al. (1982) reported that serum levels of IgM and IgG were not significantly altered in male Wistar rats dosed with 5 mg/kg/day endosulfan for 3 weeks, but resistance to infection was not tested.

Agency Contact (Chemical Manager): Jessilynn Taylor

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Endosulfan
CAS Numbers: 115-29-7
Date: June 2015
Profile Status: Final, Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 73
Species: Rat

Minimal Risk Level: ATSDR adopts the intermediate-duration oral MRL of 0.005 mg/kg/day for the chronic oral MRL, as explained below.

Reference: Banerjee BD, Hussain QZ. 1986. Effect of sub-chronic endosulfan exposure on humoral and cell-mediated immune responses in albino rats. Arch Toxicol 59:279-284.

Chronic-duration dietary studies have been conducted in rats, mice, and dogs. Studies in Wistar rats were conducted by FMC (1959b) and Hoechst (1989a), the former used 25 rats per sex per group and the latter 70 rats per sex per group. The results of Hoechst (1989a) were later published as Hack et al. (1995) with emphasis on the neoplastic effects of endosulfan. A 2-year study in NMRI mice was conducted by Hoechst (1988b) and the results were later published as Hack et al. (1995), also with emphasis on the neoplastic effects of endosulfan. A 2-year study in beagle dogs was conducted by FMC (1967) and a 1-year study was conducted by Hoechst (1989c); the former used four dogs per sex per group and the latter used six dogs per sex per group. NCI (1978) conducted long-term studies in Osborne-Mendel rats and B6C3F1 mice. These studies conducted gross and microscopic examination of organs and tissues in addition to hematology and clinical chemistry tests. All of these studies used comparable doses of technical endosulfan (up to approximately 5 mg/kg/day) except for the NCI (1978) study that used doses considerably higher in rats (up to 48 and 22 mg/kg/day, in males and females, respectively). The lowest LOAELs in rats were identified in the Hoechst (1989a) study. The most salient findings in that study included reductions in weight gain and increased incidences of marked progressive glomerulonephrosis in male and female rats from the highest-dose groups. These data are presented in Tables A-1 through A-4. The incidence of aneurysms in the kidneys of male rats was also increased, but there was no dose-response relationship (10/70, 6/70, 17/70, 10/70, and 19/70 in the control and respective increasing dose groups).

Table A-1. Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	20
0.1	70	18
0.3	70	22
0.6	70	24
2.9	70	30[a]

[a]p=0.055

Source: Hoechst 1989a

Table A-2. Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	70	1
0.1	70	6
0.4	70	6
0.7	70	5
3.8	70	8[a]

[a]p=0.017

Source: Hoechst 1989a

Table A-3. Data for the Change in Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	580	124
0.1	70	570	125
0.3	70	531	131
0.6	70	525	115
2.9	70	479[a]	94

[a]p<0.01

Source: Hoechst 1989a

Table A-4. Data for the Change in Body Weight Gain in Female Rats Exposed to Endosulfan for 2 Years

Dose (mg/kg/day)	Number of animals tested	Weight gain (g)	Standard deviation
0	70	398	105
0.1	70	350	107
0.4	70	414	85
0.7	70	363	92
3.8	70	328[a]	100

[a]p<0.05

Source: Hoechst 1989a

In mice, the highest dose tested in the Hoechst (1988b) study, 2.9 mg/kg/day, caused a significant reduction in survival rate in females (28 versus 45% in controls). No other significant treatment-related effects were reported in chronic-duration studies in mice. No significant adverse effects were reported in the 2-year study in beagle dogs that received doses of endosulfan of up to 1 mg/kg/day via the diet (FMC 1967). In the 1-year study, the dogs were fed a diet containing 0, 3, 10, or 30 ppm endosulfan (0, 0.2, 0.7, 2 mg/kg/day for males and 0, 0.2, 0.6, 1.8 mg/kg/day for females) (Hoechst 1989c). Dogs fed a diet with ≥45 ppm endosulfan were sacrificed earlier due to severe neurological effects. In the 30 ppm group, three males and two females experienced violent contractions of the abdominal muscles and upper abdomen and convulsive movements of the chap muscles 2.5–6 hours after feeding. Dogs fed the ≤30 ppm diets did not show significant treatment-related alterations in organs and tissues or in hematology values. Among clinical chemistry parameters, dogs in the ≥10 ppm diet groups showed a significant increase in mean serum alkaline phosphatase activity relative to controls (up to approximately 2-fold) beginning at 1.5 months. In the absence of significant changes in other serum enzymes and lack of treatment-related histological alterations in the liver, the investigators did not consider the changes in alkaline phosphatase activity toxicologically significant.

Of the studies mentioned above, the 2-year study in rats conducted by Hoechst (1989a) is the most appropriate for MRL derivation based on the number of animals used per group (n=70), duration of exposure that covered the entire lifespan of the animals, and identification of valid end points, such as kidney lesions and body weight changes, for which dose-response relationships could be constructed. Data sets for marked progressive glomerulonephrosis and body weight changes in male and female rats reported in the Hoechst (1989a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the four data sets to determine potential points of departure for the MRL. The data set for changes in weight gain in female rats proved not suitable for benchmark modeling even after dropping the two highest doses (out of five dose levels tested). Using the criteria for model selection mentioned earlier (see acute-duration oral MRL), the Log-logistic model (BMD_{10} 5.84 mg/kg/day; $BMDL_{10}$ 2.31 mg/kg/day) was selected as the best model to fit the incidence of marked progressive glomerulonephrosis in female rats. The Log-logistic model also provided the best fit for incidence of marked progressive glomerulonephrosis in male rats (BMD_{10} 1.17 mg/kg/day; $BMDL_{10}$ 0.56 mg/kg/day). The Exponential (Model 2) provided the best fit for the decrease in body weight gain in male rats (BMD_{10} 4.60 mg/kg/day; $BMDL_{10}$ 3.41 mg/kg/day). The results of the modeling are shown in Tables A-5, A-6, and A-7.

Table A-5. Model Predictions for Increased Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMD	Scaled residuals[b] Dose above BMD	Scaled residuals[b] Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	3	3.87	0.28	-0.09	NA	-1.61	187.00	5.39	3.01
LogLogistic[c,d]	***3***	***3.85***	***0.28***	***-0.17***	***NA***	***-1.55***	***186.84***	***5.84***	***2.31***
LogProbit[c]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Multistage (1-4 degree)[e]	3	3.85	0.28	-0.16	NA	-1.56	186.86	5.79	2.41
Probit	3	3.87	0.28	-0.10	NA	-1.60	186.98	5.47	2.94

[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]Slope restricted to ≥1.
[d]Selected model. All models, except for the LogProbit (computation failed) were fit to the data. Gamma and Weibull models were included but are not shown in the table because they defaulted to the Multistage 1 degree model. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (LogLogistic Model).
[e]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested)

Table A-6. Model Predictions for Increased Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMD	Scaled residuals[b] Dose above BMD	Scaled residuals[b] Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	3	0.72	0.87	0.50	-0.10	-0.63	441.06	1.47	0.90
LogLogistic[c,d]	***3***	***0.57***	***0.90***	***0.40***	***-0.13***	***-0.58***	***440.91***	***1.17***	***0.56***
LogProbit[c]	3	1.22	0.75	0.73	-0.06	-0.74	441.55	1.93	1.21
Multistage (1-4 degree)[e]	3	0.63	0.89	0.44	-0.12	-0.60	440.96	1.28	0.68
Probit	3	0.71	0.87	0.50	-0.10	-0.63	441.05	1.45	0.88

[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]Slope restricted to ≥1.
[d]Selected model. All models were fit to the data. Gamma and Weibull models were included but are not shown in the table because they defaulted to the Multistage 1 degree model. BMDLs for models providing adequate fit were not sufficiently close (differed by >3-fold), so the model with the lowest BMDL was selected (LogLogistic model).
[e]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested)

Table A-7. Model Predictions for Decreased Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years

Model	Test for significant difference *p*-value[a]	Variance *p*-value[b]	Mean *p*-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Linear[d]	<0.0001	0.06	0.09	0.37	NA	-1.43	3701.35	3.99	3.00
Non-constant variance									
Exponential (model 2)[e,f]	***<0.0001***	***0.43***	***0.29***	***0.30***	***NA***	***-1.33***	***3694.57***	***4.60***	***3.41***
Exponential (model 4)[e]	<0.0001	0.43	0.89	NA	NA	NA	3693.08	NA	NA
Exponential (model 5)[e]	<0.0001	0.43	0.89	NA	NA	NA	3693.08	NA	NA
Hill[e]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Linear[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39
Polynomial (2-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39
Polynomial (3-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.37
Polynomial (4-degree)[d]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.30
Power[e]	<0.0001	0.43	0.26	0.27	NA	1.36	3694.84	4.44	3.39

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1
[f]Selected model. Constant variance model did not fit variance data, but non-constant variance model did. With non-constant variance model applied, all models except for the Hill (computation failed) provided adequate fit to means. Although the Exponential 4 and 5 models provided adequate fit to the means, the BMD and BMDL computations failed. BMDLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 2 model; the Exponential 3 converged onto the Exponential 2).

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable (BMDL computation failed or the BMD was higher than the highest dose tested); SD = standard deviation

The lower $BMDL_{10}$ of 0.56 mg/kg/day is more health protective and is selected as the point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 0.56 mg/kg/day results in a chronic-duration oral MRL of 0.006 mg/kg/day for endosulfan. Since this MRL is slightly higher than the intermediate-duration oral MRL of 0.005 mg/kg/day derived for endosulfan, the intermediate-duration oral MRL, which is protective of potential effects due to chronic exposure to endosulfan, is adopted also for the chronic-duration oral MRL for endosulfan.

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

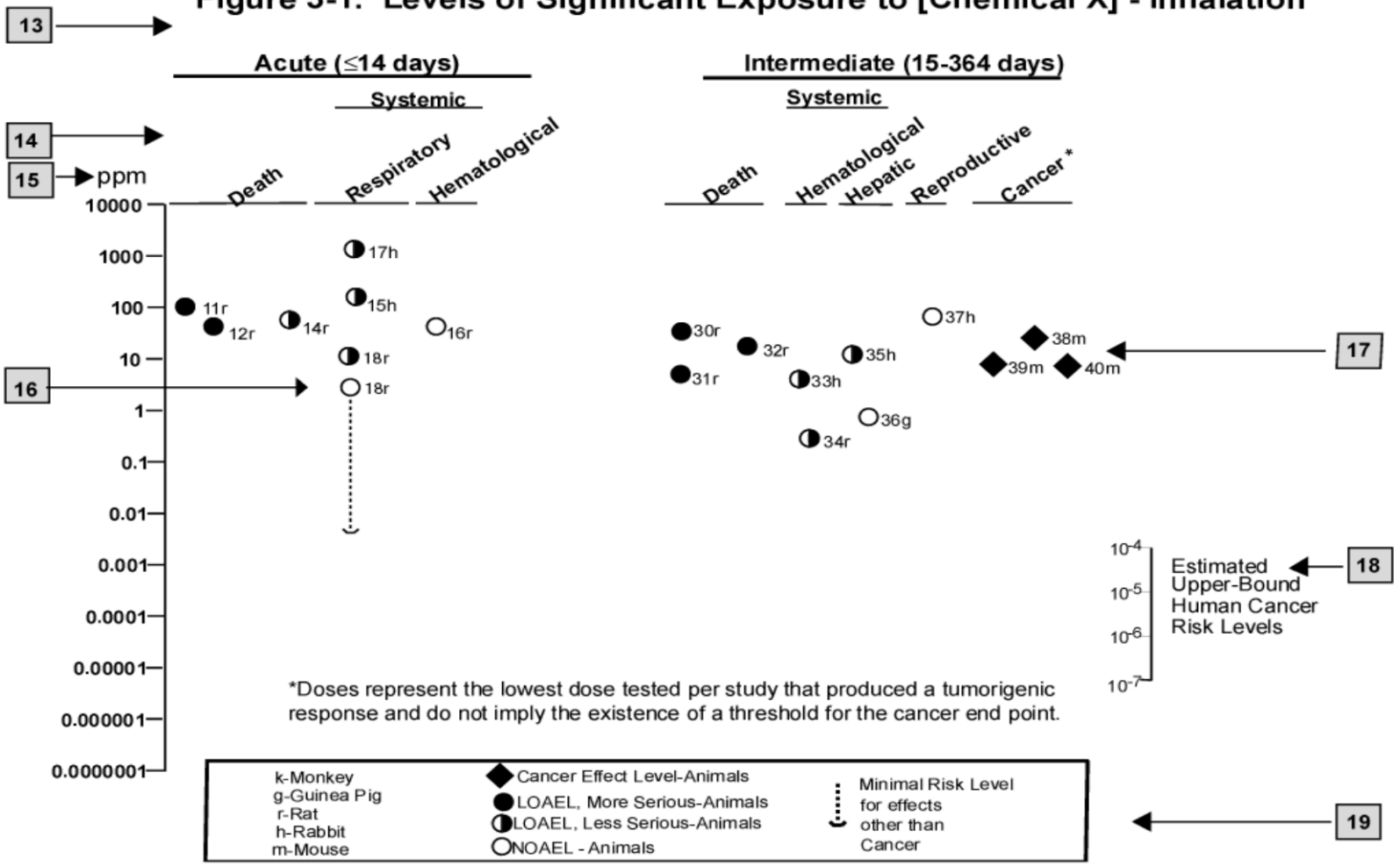
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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/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
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/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	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