APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cresols
CAS Numbers: 95-48-7, 108-39-4, 106-44-5, 1319-77-3
Date: July 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 55
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: NTP. 1992b. NTP report on the toxicity studies of cresols (CAS Nos. 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. NIH Publication No. 92-3128. NTP Tox 9.

Experimental design: Groups of Fischer 344 rats (20/sex/group) were administered *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) in the diet at levels of 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm for 13 weeks (NTP 1992b). The corresponding doses of test compound estimated by the investigators were 0, 123, 241, 486, 991, and 2,014 mg/kg/day for males and 0, 131, 254, 509, 1,024, and 2,050 mg/kg/day for females. End points evaluated included clinical signs, food consumption, organ weights, clinical chemistry and hematology, and gross and microscopic appearance of organs and tissues. Although the dose groups consisted of 20 rats of each sex, 10 males and 10 females were used for clinical chemistry, hematology, and urinalysis studies and the remaining 10 rats/sex/group were used in gross pathology, organ weight, and histopathological studies.

Effect noted in study and corresponding doses: There were no deaths during the study. Final body weight in the 2,014/2,050 mg/kg/day males and females was reduced 17 and 12%, respectively, relative to controls. Food consumption was also reduced (about 10%) in this group during the first week of the study. Additionally, males and females in this group exhibited rough hair coat; females also had a thin appearance. Absolute and relative liver weights were significantly increased (11–12%) in males at 486 mg/kg/day and in females at 1,024 mg/kg/day. Absolute and relative kidney weight were increased in males at 991 mg/kg/day. In general, hematology findings were unremarkable, although there was a tendency to hemoconcentration at 2,014/2,050 mg/kg/day early in the study. Clinical chemistry tests showed an increase in serum alanine aminotransferase (ALT) in males and females exposed to 2,014/2,050 mg/kg/day and in sorbitol dehydrogenase (SDH) in males at 2,014 mg/kg/day only on day 5. Bile acids in serum were increased in females at 2,050 mg/kg/day on day 90 and at 241 and 991 mg/kg/day in males also on day 90. There was no indication of renal injury as judged by the results of urinalyses. Significant histopathological changes included minimal bone marrow hypocellularity in males and females at 2,014/2,050 mg/kg/day, and increased colloid (minimal) in thyroid follicular cells in females at 509 mg/kg/day and in males at 15,000 ppm (991 mg/kg/day). An increased dose-related incidence and severity of hyperplasia and glandular hyperplasia of the nasal respiratory epithelium was observed in male and female rats. Severity was minimal at 123/131 mg/kg/day, mild at 486/509 mg/kg/day, and moderate at 2,014/2,050 mg/kg/day. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The incidences in males dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. A similar trend was seen in female rats, but 3/10 control females also exhibited hyperplasia (3/10, 1/10, 5/10, 9/10, 8/10, and 10/10 at 0, 131, 254, 509, 1,024, and

2,050 mg/kg/day, respectively). The LOAELs for nasal lesions in male and female rats were 123 and 254 mg/kg/day, respectively. The NOAEL in females was 131 mg/kg/day and no NOAEL was established in males.

In the 28-day study with *m/p*-cresol in rats, the incidences of hyperplasia of the nasal respiratory epithelium in females dosed with 0, 27, 95, 268, 886, and 2,570 mg/kg/day were 0/5, 0/5, 3/4, 5/5, 5/5, and 5/5, respectively. However, data from the 13-week study are preferred for MRL derivation because of the longer duration and because only five rats/group were examined in the 28-day study.

Data from the NTP (1992b) were considered adequate for analysis using the benchmark dose approach for MRL derivation. Benchmark dose models in the EPA Benchmark Dose Software (BMDS) (version 2.0) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL (details of the modeling are presented below).

Dose and end point used for MRL derivation: $BMDL_{10}$ of 13.94 mg/kg/day for nasal lesions in male rats.

[ ] NOAEL [ ] LOAEL [x] $BMDL_{10}$

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Conversion from diet to dose was done by the investigators.

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: Almost all of the information available on health effects from intermediate-duration oral exposure is derived from a comprehensive study in rats and mice administered the three cresol isomers and a cresol mixture for 28 days and 13 weeks (NTP 1992b). There are also two multigeneration reproductive studies in mice dosed with *o*-cresol (NTP 1992a) and a cresol mixture (NTP 1992c). Evaluation of the results of these studies indicates that the most sensitive end point was the nasal respiratory epithelium of rats and mice dosed with *p*-cresol or an *m/p*-cresol mixture. No clear target of toxicity emerged for *o*- or *m*-cresol. The nasal lesions occurred in rats dosed with *p*-cresol for 28 days (≥770 mg/kg/day), in rats exposed to *m/p*-cresol for 28 days (≥95 mg/kg/day), in mice exposed to *p*-cresol for 28 days (≥163 mg/kg/day), in mice exposed to *m/p*-cresol for 28 days (≥604 mg/kg/day), in rats exposed to *m/p*-cresol for 13 weeks (≥123 mg/kg/day), and in mice exposed to *m/p*-cresol for 13 weeks (≥472 mg/kg/day). Other effects that occurred at higher doses included increases in liver and kidneys weights (≥240 mg/kg/day), bone marrow hypocellularity (≥2,000 mg/kg/day), and mild uterine atrophy (≥1,000 mg/kg/day) (NTP 1992b). Clinical tests of liver and kidney function were generally unremarkable and gross and microscopic evaluation of the liver and kidney showed no significant alterations (NTP 1992b). None of the intermediate-duration oral gavage studies examined the nasal respiratory epithelium of the animals, and neither did the two multigeneration reproductive dietary studies in mice (NTP 1992a, 1992c).

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APPENDIX A

BENCHMARK MODELING OF NASAL RESPIRATORY LESIONS IN RATS

Benchmark dose models in the EPA Benchmark Dose Software (BMDS version 2.0) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL. $BMDL_{10}$s (i.e., 95% lower confidence limits on the model-estimated dose associated with a 10% extra risk for nasal lesions) calculated with the best-fitting models for each data set (see Tables A-1, A-2, and, A-3 and Figures A-1 and A-2) were 13.9 mg/kg/day for males and 30.8 mg/kg/day for females. While this difference in benchmark dose may indicate that male rats are more sensitive than females, it also can be a statistical artifact of a rather small sample size, only 10 rats per group. The male rat data set was selected for determining the point of departure for MRL derivation in order to be public health protective.

Table A-1. Incidence Data for Respiratory Epithelium Glandular Hyperplasia or Hyperplasia in Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

	Dietary concentration (ppm)	Dose (mg/kg/day)	Incidence of nasal lesions
Male	0	0	0/10
	1,880	123	3/10
	3,750	241	8/10
	7,500	486	10/10
	15,000	991	9/10
	30,000	2,014	10/10
Female	0	0	3/10
	1,880	131	2/10
	3,750	254	6/10
	7,500	509	10/10
	15,000	1,024	8/10
	30,000	2,050	10/10

Source: NTP 1992b

Table A-2. Goodness-of-Fit Statistics and BMD_{10}s and $BMDL_{10}$s from Models Fit to Incidence Data for Nasal Lesions in Male Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

Model	AIC	X^2 p value[a]	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma	37.3167	0.1221	24.1138	16.7698
Logistic	46.7819	0.0000	63.9362	42.8254
Log-Logistic[b]	**36.8962**	**0.2605**	**55.8863**	**13.9381**
Multistage	37.3167	0.1221	24.1138	16.7698
Probit	49.738	0.0002	71.306	50.8541
Log-probit	37.6831	0.2511	46.1987	26.6915
Quantal-linear	37.3167	0.1221	24.1138	16.7698
Weibull	37.3167	0.1221	24.1138	16.7698

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test

Source: NTP 1992b

Table A-3. Goodness-of-Fit Statistics and BMD_{10}s and $BMDL_{10}$s from Models Fit to Incidence Data for Nasal Lesions in Female Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

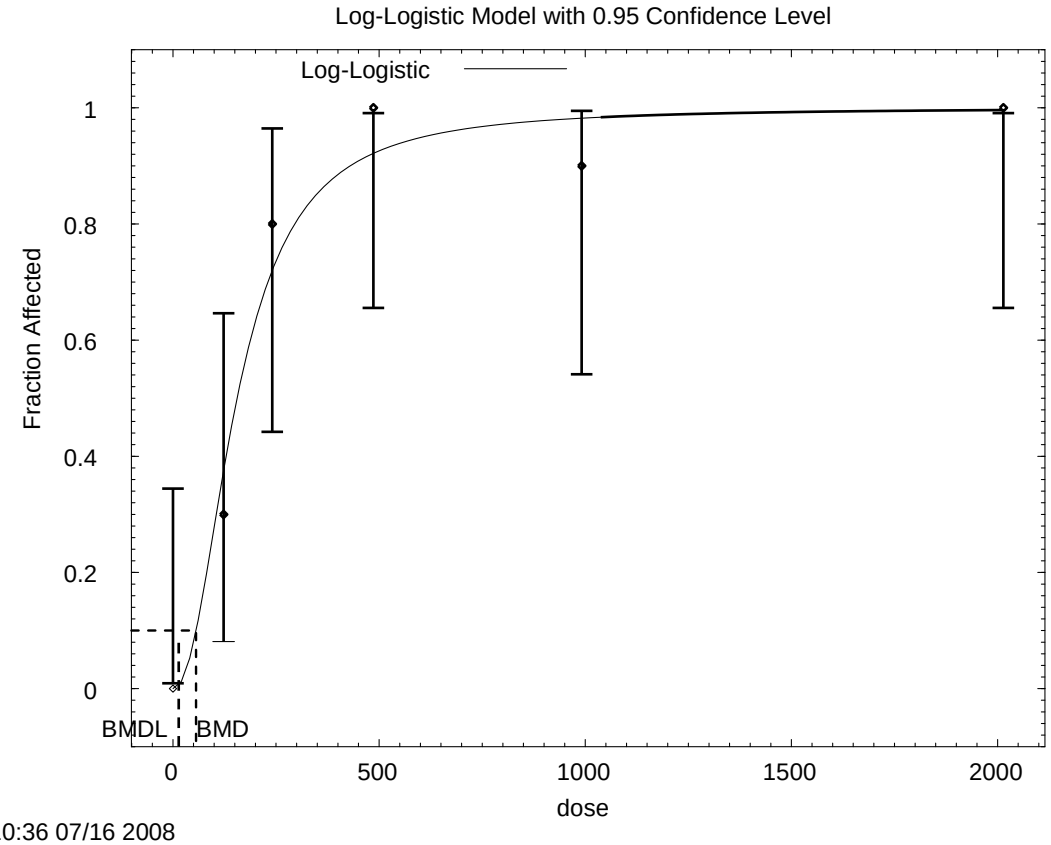
Model	AIC	X^2 p value[a]	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma	61.5191	0.0477	64.2166	30.9781
Logistic	60.7552	0.0557	89.5533	60.4852
Log-Logistic	60.0961	0.0487	98.7921	28.7889
Multistage[b]	**59.5988**	**0.1020**	**48.0244**	**30.7916**
Probit	61.2978	0.0600	98.0573	69.3757
Log-probit	60.351	0.0591	99.9316	51.3824
Quantal-linear[b]	**59.5988**	**0.1020**	**48.0246**	**30.7916**
Weibull	61.5874	0.0505	52.5879	30.8181

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test

Source: NTP 1992b

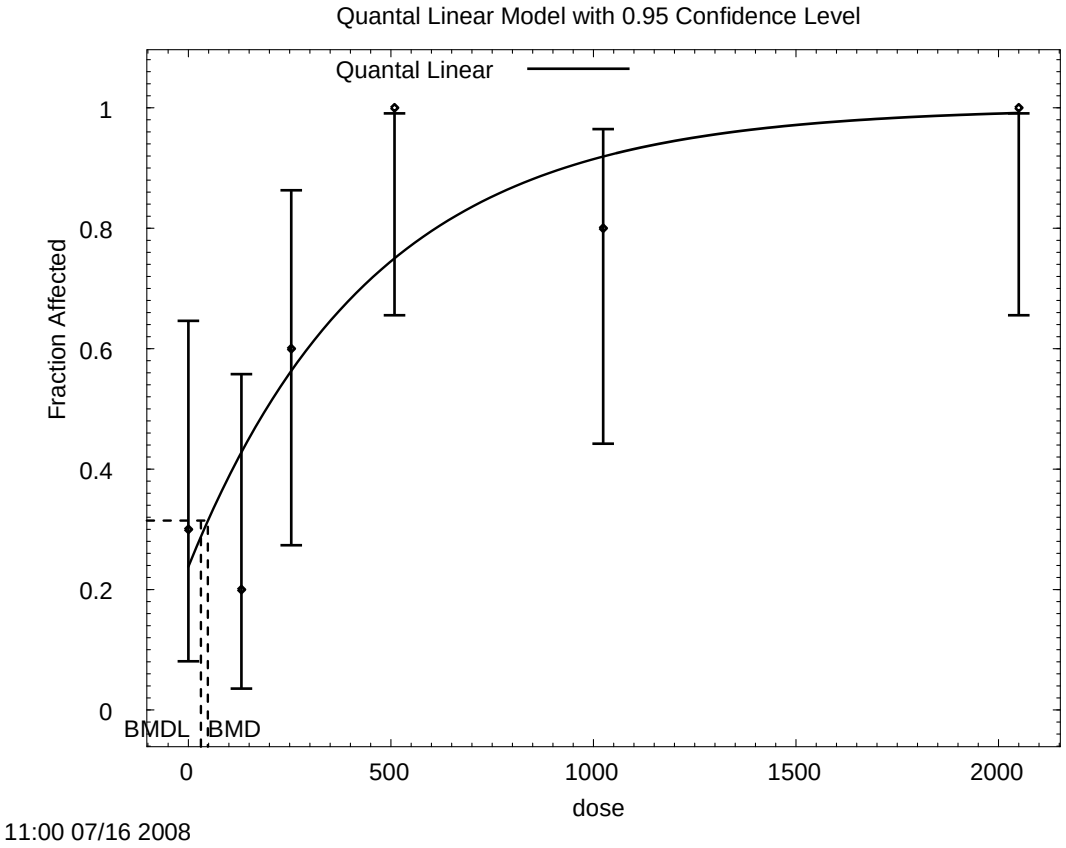
Figure A-1. Observed and Predicted Incidences of Nasal Lesions in Male Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 1992b

Figure A-2. Observed and Predicted Incidences of Nasal Lesions in Female Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks*



*BMDs and BMDLs Indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 1992b

BMDs and BMDLs associated with 1, 5, 10, 20, and 30% extra risk were calculated with the best-fitting model of the male rat nasal lesion incidence data (see Table A-4). Following EPA's Benchmark Dose Guidance (EPA 2000a) to select a point of departure, a benchmark response (BMR) of 10% was selected for the benchmark analysis of nasal lesion incidence data in male rats in the 13-week NTP (1992b) study. The BMD corresponding to a BMR of 10% extra risk is 55.89 mg/kg/day; the corresponding $BMDL_{10}$ is 13.94 mg/kg/day (see Table A-4). Applying an uncertainty factor of 100 (10 each for intra- and interspecies extrapolation) to the $BMDL_{10}$ yields an intermediate-duration oral MRL of 0.1 mg/kg/day for *m/p*-cresol.

Table A-4. Best-fitting Model Predictions for 1, 5, 10, 20, and 30% Extra Risk for Incidence of Nasal Lesions Observed in Rats Exposed to *m/p*-Cresol in the Feed for 13 Weeks

Best fitting model	BMR (% extra risk)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male: Log-Logistic	1	18.38	1.70
	5	39.52	7.26
	10	**55.89**	**13.94**
	20	81.41	28.08
	30	104.53	44.35
Female: Quantal Linear	1	4.58	2.94
	5	23.38	14.99
	10	48.02	30.79
	20	101.71	65.21
	30	162.58	104.24

Source: NTP 1992b

All available dichotomous models in the EPA BMDS (version 2.0) were fit to the incidence data for nasal lesions (respiratory epithelium glandular hyperplasia or hyperplasia) in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks (NTP 1992b) (Table A-1). Predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated.

Male Rats

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of nasal lesions in male rats (x^2 p value $\geq$0.1) (Table 2). Comparing across models, a better fit is indicated by a lower Aikake's Information Criteria value (AIC) (EPA 2000a). The log-logistic model was determined to be the best-fitting model, as indicated by the AIC (Table A-2). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 30, 20, 10, 5, and 1, calculated from the best fitting model, are shown in Table A-4.

The form and parameters of the log-logistic model for the male rat data are as follows:

P[response] = background + (1-background)/[1+EXP(-intercept-slope*Log(dose))]
background = 0;
intercept = -5.78913;
slope = 1.21882.

Female Rats

As assessed by the chi-square goodness-of-fit test, only the quantal linear model (which was the similar to the 1-degree polynomial model) provided an adequate fit to the data for the incidence of nasal lesions in female rats (x^2 p value $\geq$0.1). Therefore, the quantal linear model was determined to be the best-fitting model (Table 3). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 30, 20, 10, 5, and 1%, calculated from the quantal linear model, are shown in Table A-4.

The form and parameters of the quantal linear model for the female rat data are as follows:

P[response] = background + (1-background)*[1-EXP(-slope*dose)]

background = 0.318182;
slope = 0.001321;
Power = 1 (Specified)

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cresols
CAS Numbers: 95-48-7, 108-39-4, 106-44-5, 1319-77-3
Date: July 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 130
Species: Mice

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: NTP. 2008. Toxicology and carcinogenesis studies of cresols (CAS No. 1319-77-3) in male F344/N rats and female B6C3F_1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. TR-550. Draft technical report.

Although the report has not yet been finalized by the NTP, a draft technical report has been reviewed by the NTP Board of Scientific Counselors Technical Reports Review Subcommittee, and a draft abstract, pathology tables, and survival and growth curves are available in the NTP web site (http://ntp.niehs.nih.gov/index.cfm?objectid=9B58ADF7-F1F6-975E-78A23152B1596409).

Experimental design: Groups of female B6C3F_1 mice (50/group) were administered *m/p*-cresol (60% *m*-cresol, 40% *p*-cresol) in the diet at levels of 0, 1,000, 3,000, or 10,000 ppm for 2 years (NTP 2008). The corresponding doses of test compound estimated by the investigators were approximately 0, 100, 300, and 1,040 mg/kg/day. End points evaluated included clinical signs, food consumption, organ weights, and gross and microscopic appearance of organs and tissues at termination.

Effect noted in study and corresponding doses: Dosing with *m/p*-cresol did not affect survival rate. Food consumption did not appear to vary significantly throughout the study. No significant treatment-related clinical signs were reported. At termination, body weight in the mid- and high-dose groups was significantly lower than controls (11 and 24%, respectively). Significant treatment-related, non-neoplastic effects included: minimal to moderate bronchiolar hyperplasia in the lung (0/50, 42/50/, 44/49, 47/50); minimal to mild hyperplasia of the nasal respiratory epithelium (0/50, 0/50, 28/49, 21/50); mild follicular degeneration of the thyroid gland (7/48, 24/48, 24/49, 21/50); and increased eosinophilic foci in the liver (1/50, 0/50, 2/49, 12/50). NOAELs for bronchiolar hyperplasia and thyroid follicular degeneration were not established, and in both cases, the LOAEL was 100 mg/kg/day.

Since the incidence data indicate that bronchiolar hyperplasia of the lung and follicular degeneration of the thyroid gland had lower thresholds than the liver or nasal effects, the former two responses were considered for analysis using the benchmark dose approach for MRL derivation. After inspection of the dose response data, the use of a LOAEL/NOAEL approach for MRL derivation was considered to be more appropriate than the use of benchmark dose analysis because of the steep increase in the response rates between the control group and the first exposure level.

Dose and end point used for MRL derivation: LOAEL of 100 mg/kg/day for bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice.

[ ] NOAEL [x] LOAEL [ ] $BMDL_{10}$

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Conversion from diet to dose was done by the investigators.

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: The NTP (2008) is the only chronic-duration study with cresols available. The NTP (2008) also tested male F-344/N rats and the results showed that the most sensitive end point was the nasal respiratory epithelium, as in the shorter-term studies (NTP 1992b). Other less sensitive effects observed in rats included hyperplasia of the transitional epithelium of the renal pelvis, squamous metaplasia in the nasal respiratory epithelium, inflammation of the nose, and eosinophilic foci in the liver. The incidence of respiratory epithelium hyperplasia of minimal to mild severity was 3/50, 17/50, 31/50, and 47/50 in the control, low-, mid-, and high-dose groups, respectively. As discussed in Section 2.3, the data suggest that, over the range of doses used in the NTP (1992b, 2008) studies, exposure beyond 13 weeks had little or no effect on the incidence or severity of the nasal respiratory hyperplasia, indicating that the intermediate-duration MRL, which is based on incidence data for this lesion, should be protective of nasal lesions induced by chronic-duration exposure. This is supported by the fact that fitting the incidence data for nasal respiratory epithelium hyperplasia from the 2-year study to the same BMDS model (Log-Logistic) that provided the $BMDL_{10}$ used to derive the intermediate-duration oral MRL yields a $BMDL_{10}$ for chronic exposure to *m/p*-cresol of 13.9017 mg/kg/day, essentially the same as the $BMDL_{10}$ of 13.9381 mg/kg/day used to derive the intermediate-duration oral MRL for *m/p*-cresol.

Agency Contacts (Chemical Managers): Malcolm Williams, Ph.D.; John Risher, Ph.D.; Mike Fay, Ph.D.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

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

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

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

SAMPLE

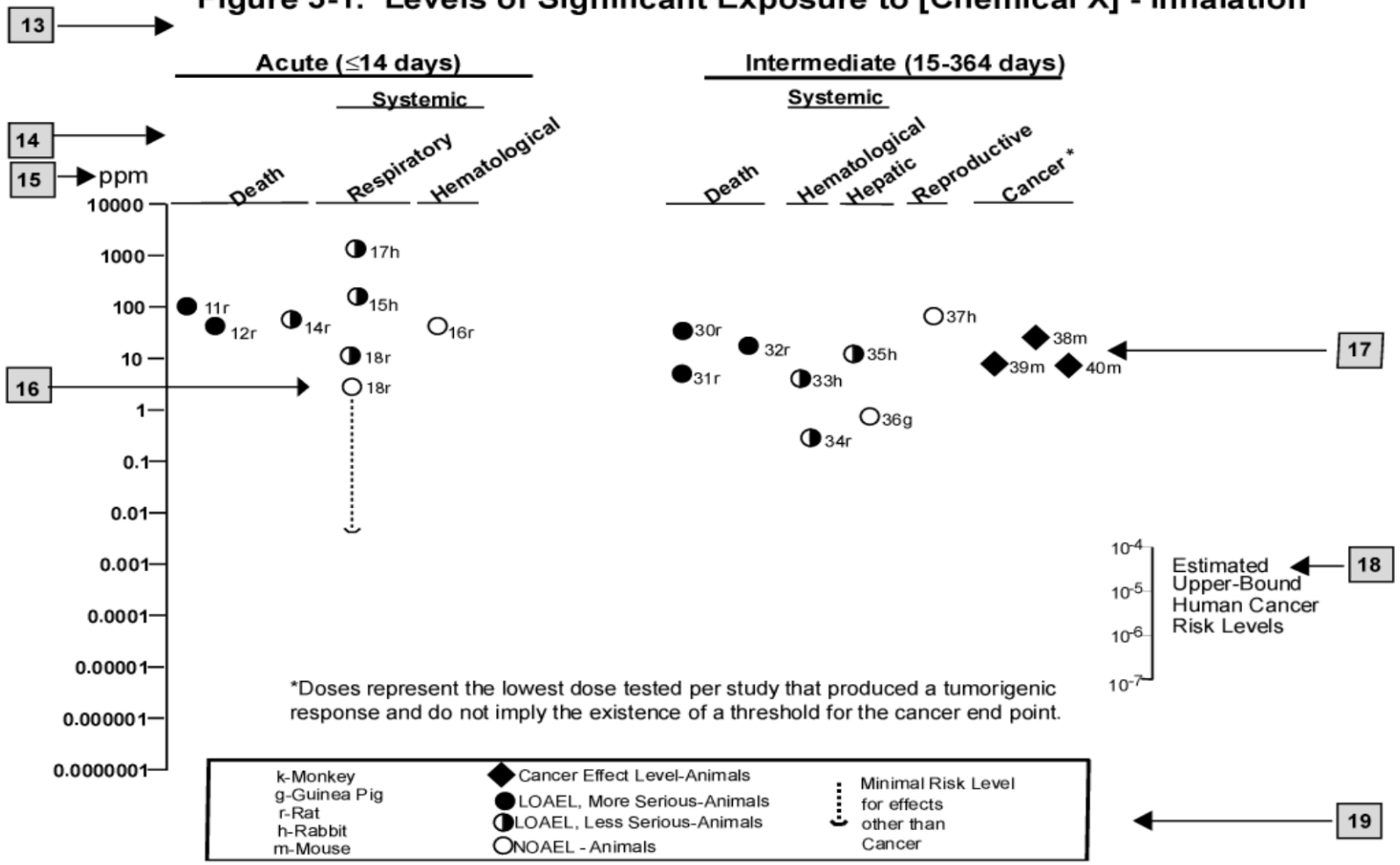
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

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

SAMPLE

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



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

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

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

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APPENDIX D. INDEX