# 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 30333.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2,4-Trichlorobenzene
CAS Number: 120-82-1
Date: May 2014
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 21
Species: Rat

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

Reference: CMA. 1989. A three month dietary range-finding study of 1,2,4-trichlorobenzene in rats final report with letter dated 2/2/89 from Chemical Manufacturers Association. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. EPA Document No. 40-98201006. OTS0523023.

Experimental design: Groups of Fisher-344 rats (10/sex/group) were fed a diet containing 0, 200, 600, or 1,800 ppm 1,2,4-trichlorobenzene for 14 weeks; this diet provided doses of 0, 14.6, 45.6, or 133.7 mg/kg/day for males and 0, 17, 52.5, or 150.6 mg/kg/day for females. These doses were calculated by dividing the sum of the weekly doses provided by the investigators by 14 weeks. End points monitored included clinical signs (daily), physical examination (weekly), ophthalmology (initiation and termination), body weight and food consumption (weekly), hematology and clinical chemistry (termination), gross necropsy (all rats at termination), selected organ weights, and histopathology of all major organs and tissues of the control and high-dose group and liver and kidney of the low- and mid-dose groups.

Effect noted in study and corresponding doses: Treatment with 1,2,4-trichlorobenzene did not affect survival rate. Clinical signs were limited to chromodacryorrhea and lacrimation, which occurred more frequently in treated groups, but without dose-response. The test for ocular abnormalities did not reveal compound-related effects. Administration of 1,2,4-trichlorobenzene did not significantly affect body weight or weight gain. Food consumption was significantly higher in the mid- and high-dose groups than in controls. Hematological alterations consisted of decreased mean erythrocyte count (5%), hemoglobin (7%), and hematocrit (5%) in males dosed with 133.7 mg/kg/day and decreased hemoglobin (4%) and hematocrit (4%) in females dosed with 150.6 mg/kg/day. These changes are within the normal range and are not considered biologically significant. Platelets were significantly increased (16%) in males dosed with 133.7 mg/kg/day; the toxicological significance of this finding is unclear. Significant clinical chemistry changes included elevated BUN in high-dose males (12%) and females (20%), elevated total protein, albumin, and calcium in high-dose males, and lower serum AST activity in males dosed with 45.6 mg/kg/day (22%) and 133.7 mg/kg/day (28%). The elevated BUN was consistent with microscopic alterations in kidneys from male rats. The clinical significance of the alterations in protein and calcium were unclear and the lower transaminase activity was not considered of biological significance. Significant changes in organ weight included dose-related increases in absolute and relative liver weight in all male groups and in mid- and high-dose females, and increased absolute and relative kidneys weight and absolute testes weight in males dosed with 133.7 mg/kg/day. No compound-related gross lesions were observed. Histopathological alterations were limited to the kidneys and liver. Kidney lesions were evident in males dosed with 45.6 and 133.7 mg/kg/day and consisted of dilated tubules, granular casts, hyaline droplets, interstitial nephritis, and papillary mineral deposition. In the liver, centrilobular hepatocyte hypertrophy occurred in males dosed with 45.6 and 133.7 mg/kg/day (0/10, 0/10, 5/10, and 10/10) and in females dosed with 150.6 mg/kg/day (0/10, 0/10, 0/10, and 10/10). Hepatocyte hypertrophy

was the probable cause of the increases in liver weight. Liver changes were more prominent in males than in females.

Data for renal effects in male rats were not considered for MRL derivation due to the strong possibility that this may be a unique response of the male rat and not relevant for quantitative risk assessment (EPA 1991). Specific indications that this may be the case include the increased incidences of hyaline droplets, granular casts, and tubule dilation, and the fact that none of these lesions occurred in female rats. In addition, since there is not enough evidence to dissociate the interstitial nephritis from the male-specific nephropathy, interstitial nephritis was also not considered for modeling. In support of this position is the fact that interstitial nephritis did not occur in female rats.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 14.35 mg/kg/day for centrilobular hepatocyte hypertrophy in male rats.

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

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, 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? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The liver was also a target in an additional 3-month study in rats and in a 13-week study in mice. The study in Sprague-Dawley rats evaluated hematology, clinical chemistry and histopathology of the major organ and tissues, and reported histological alterations in the liver, kidneys, and thyroid in the various dose groups (doses ranged from 0.07 to 82 mg/kg/day in males and from 0.11 to 101 mg/kg/day in females) (Côté et al. 1988). However, the investigators provided only a qualitative description of the results regarding histopathology. In that study, high-dose males showed increases of 13 and 20% in absolute and relative liver weight, respectively, and of 31 and 36% in absolute and relative kidneys weight, respectively. Hematology and clinical chemistry tests were unremarkable. In the 13-week study in mice, groups of $B6C3F_1$ mice (10/sex/group) were administered a diet that provided doses of 0, 67, 850, or 1,222 mg/kg/day to males and 0, 86, 1,183, or 1,345 mg/kg/day to females (Hiles 1989). End points monitored included clinical signs twice daily and body weight and food consumption weekly. Hematology and clinical chemistry tests were conducted at initiation and during week 14. At termination, gross necropsy was conducted, selected organs were weighed, and selected tissues were examined microscopically. The lungs, liver, and kidneys from all groups were examined; other organs from only the control and high-dose group were examined. Final body weight was significantly reduced in high-dose males (9%) and females (8.3%). Cumulative body weight gain was significantly reduced in low-dose males (27%), high-dose males (40%) and high-dose females (33%); these changes were associated with significant reductions in food consumption throughout the study. Ophthalmologic examinations were conducted at initiation and termination. Significant, treatment-related alterations occurred only in the liver from males dosed with ≥850 mg/kg/day and females dosed with ≥1,183 mg/kg/day; the

respective NOAELs were 67 and 86 mg/kg/day. The lesions consisted of hepatocellular cytomegaly with karyomegaly and hepatocellular atrophy and degeneration. The incidences in males and females were 0/10, 0/10, 10/10, and 10/10 and 0/9, 0/10, 10/10, and 9/9, respectively (one control female and one high-dose female were accidentally killed during the study).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

## BENCHMARK MODELING OF HEPATOCELLULAR HYPERTROPHY IN MALE RATS

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the incidence data for centrilobular hepatocyte hypertrophy in male rats from the CMA (1989) study. Only incidences in males were modeled (0/10, 0/10, 5/10, 10/10); incidences in females (0/10, 0/10, 0/10, 10/10) were judged not amenable for benchmark analysis. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. 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 benchmark response (BMR). Among all of the models providing adequate fit to the data, the BMDL from the model with the lowest AIC is chosen. The Gamma model was selected for MRL derivation (Table A-1).

## Table A-1. Model Predictions for the Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats Exposed to 1,2,4-Trichlorobenzene

| Model | $\chi^2$ Goodness of fit p-value[a] | AIC | $BMD_{10}$ (mg/kg/day) | $BMDL_{10}$ (mg/kg/day) |
|---|---|---|---|---|
| **Gamma[b,c]** | **1.00** | **15.86** | **33.09** | **14.35** |
| Logistic | 1.00 | 17.86 | 41.94 | 18.95 |
| Log-Logistic[d] | 1.00 | 17.86 | 40.29 | 16.74 |
| Log-Probit[d] | 1.00 | 17.86 | 35.74 | 16.04 |
| Multistage (1-degree)[e] | 0.26 | 23.05 | 6.43 | 4.04 |
| Multistage (2-degree) | 0.85 | 17.29 | 18.59 | 8.90 |
| Multistage (3-degree) | 0.97 | 16.31 | 24.71 | 10.07 |
| Probit | 1.00 | 17.86 | 38.66 | 17.28 |
| Weibull[b] | 1.00 | 17.86 | 37.74 | 13.40 |
| Quantal-Linear | 0.26 | 23.05 | 6.43 | 4.04 |

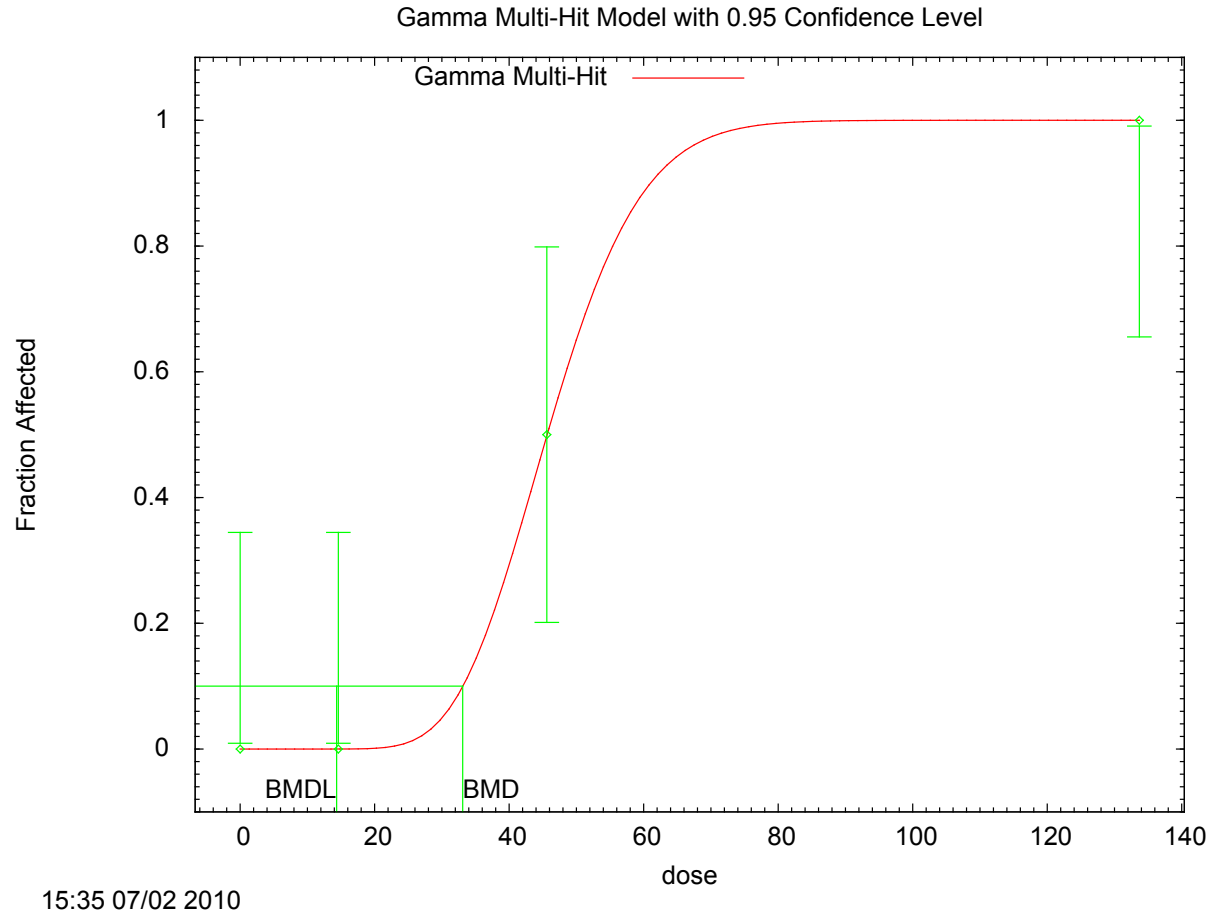
[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Best-fitting model. Among models with adequate fit, the model with the lowest AIC was selected (Gamma).
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: CMA 1989

The dose-response curve is shown in Figure A-1.

**Figure A-1. Fit of Gamma Model to Data on 1,2,4-Trichlorobenzene, Incidence of Centrilobular Hepatocyte Hypertrophy in Male Rats**




Source: CMA 1989

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2,4-Trichlorobenzene
CAS Number: 120-82-1
Date: May 2014
Profile Status: Final Post-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 38
Species: Rat

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

Reference: Moore MR. 1994a. Final report (6 copies), 104-week dietary carcinogenicity study with 1,2,4-trichlorobenzene in rats, with cover letter dated 6/15/94. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. EPA Document No. OPPTS-44612. OTS0558832.

Experimental design: Groups of Fisher-344 rats (50/sex/group) were fed a diet containing 0, 100, 350, or 1,200 ppm 1,2,4-trichlorobenzene for 104 weeks. The diet provided doses of 0, 5.6, 19.4, or 66.5 mg/kg/day 1,2,4-trichlorobenzene to males and 0, 6.9, 23.5, or 81.4 mg/kg/day 1,2,4-trichlorobenzene to females. Parameters evaluated included mortality (twice daily), clinical signs, body weight and food consumption (weekly for 16 weeks and every 4 weeks thereafter), hematology (week 52 and 78 for cellular morphology and leukocyte differential, from control and high-dose groups), organ weight (at termination, brain, brainstem, liver, kidneys, testes and epididymis), and gross necropsy and histological examination of all major organs and tissues at termination.

Effect noted in study and corresponding doses: Treatment with 1,2,4-trichlorobenzene resulted in a significant reduction in survival rate in males dosed with 66.5 mg/kg/day. Survival rate in the control, 5.6, 19.4, and 66.5 mg/kg/day males at week 104 were 84, 80, 84, and 60% respectively. There were no distinct or pronounced compound-related differences in clinical signs between treated and control groups. Differences in body weight between treated and control rats were <10% throughout the study. Food consumption was decreased 4–7% in treated groups relative to controls during the study. The only statistically significant hematology findings were a decrease in basophiles at week 52 and monocytes at week 105 in males dosed with 66.5 mg/kg/day, which the investigators considered minor. No evidence of leukemia was noted. Gross necropsy at termination showed increased incidence of liver and kidney abnormalities in males dosed with 19.4 and 66.5 mg/kg/day and a slight increase in incidence of uterine masses in treated females relative to controls; these changes were not discussed any further. Significant changes in organ weight were limited to an increase in absolute and relative liver weight in both male and female rats receiving the highest doses of 1,2,4-trichlorobenzene and a decrease in absolute and relative testes weight in males dosed with 5.6 and 19.4 mg/kg/day. Treatment-related histological alterations were restricted to the liver of males and females and to the kidneys of males and consisted of the following: hepatocellular hypertrophy (which probably caused the increase in liver weight), focal cystic degeneration, diffuse fatty change, transitional renal cell hyperplasia, and increased severity of chronic rat nephropathy in males. Incidences of liver lesions are presented in Table A-2 (note that a smaller number of animals from the low-dose groups were examined for histopathology).

## Table A-2. Incidence of Liver Lesions in Rats in a 104-Week Dietary Study

| | | | | |
|---|---|---|---|---|
| Males | | | | |
| Dose (mg/kg/day) | 0 | 5.6 | 19.4 | 66.5 |
| Hepatocellular hypertrophy | 2/50(4%) | 1/26(3.8%) | 5/50(10%) | 30/50(60%) |
| Focal cystic degeneration | 9/50(18%) | 3/26(11.5%) | 4/50(8%) | 19/50(38%) |
| Diffuse fatty change | 5/50(10%) | 3/26(11.5%) | 5/50(10%) | 14/50(28%) |
| Females | | | | |
| Dose (mg/kg/day) | 0 | 6.9 | 23.5 | 81.4 |
| Hepatocellular hypertrophy | 6/50(12%) | 5/25(20%) | 5/50(10%) | 37/50(74%) |
| Diffuse fatty change | 15/50(30%) | 6/25(24%) | 21/50(42%) | 30/50(60%) |

Source: Moore 1994a

The incidences of transitional cell hyperplasia in the kidneys of male rats were as follows: 0/50, 0/19, 2/50, and 34/50 in males dosed with 0, 5.6, 19.4, and 66.5 mg/kg/day 1,2,4-trichlorobenzene, respectively. Since there is strong evidence from the 14-week study (CMA 1989) suggesting that the renal lesions in male rats may represent a male-specific response not relevant for MRL derivation, and that the renal cell hyperplasia reported in the 104-week study is a typical response seen in the male rat nephropathy, renal cell hyperplasia was not considered as a potential end point for MRL derivation.

Table A-2 shows that: (1) diffuse fatty change was significantly increased in males and females only at the highest dose; (2) focal cystic degeneration occurred at lower incidence in the low- and mid-dose males compared to controls, and was significantly increased only at the highest dose; (3) hepatocellular hypertrophy in female rats occurred at increased frequency only at the highest dose; and (4) only hepatocellular hypertrophy in male rats exhibited dose-response characteristics. Based on these facts, only the hepatocellular hypertrophy in male rats was considered for MRL derivation.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 13.33 mg/kg/day for hepatocellular hypertrophy in male rats.

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

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, 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? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Treatment of $B6C3F_1$ mice with 1,2,4-trichlorobenzene in the diet for 104 weeks produced hepatocellular carcinoma (Moore

1994b). Two intermediate-duration studies in rats and one in mice also suggested that the liver is a target for 1,2,4-trichlorobenzene (CMA 1989; Côté et al. 1988; Hiles 1989).

Agency Contacts (Chemical Managers): Obaid Faroon, D.V.M., Ph.D.

**BENCHMARK MODELING OF HEPATOCELLULAR HYPERTROPHY IN MALE RATS**

Models in the EPA Benchmark Software (BMDS version 2.1) were fit to the data set for hepatocellular hypertrophy in the liver of male rats. A BMR of 10% was selected in the absence of data that would support a lower BMR. In accordance with EPA (2000a) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. 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 BMDL from the model with the lowest AIC is chosen. Details of the modeling are presented below in Table A-3 and Figure A-2.

**Table A-3. Model Predictions for the Incidence of Hepatocellular Hypertrophy in Male Rats**

| Model | $\chi^2$ Goodness of fit *p*-value[a] | AIC | $BMD_{10}$ (mg/kg/day) | $BMDL_{10}$ (mg/kg/day) |
|---|---|---|---|---|
| Gamma[b] | 0.92 | 131.09 | 23.40 | 13.76 |
| Logistic | 0.95 | 129.18 | 25.44 | 20.54 |
| Log-Logistic[c] | 0.91 | 131.10 | 23.34 | 14.03 |
| Log-Probit[c] | 0.96 | 131.08 | 22.72 | 14.39 |
| Multistage (1-degree)[d] | 0.06 | 135.48 | 10.13 | 7.62 |
| **Multistage (2-degree)[d,e]** | **0.98** | **129.12** | **23.25** | **13.33** |
| Multistage (3-degree)[d] | 0.87 | 131.11 | 23.94 | 13.02 |
| Probit | 0.92 | 129.24 | 22.92 | 18.65 |
| Weibull[b] | 0.88 | 131.11 | 23.95 | 13.62 |
| Quantal-Linear | 0.06 | 135.48 | 10.13 | 7.62 |

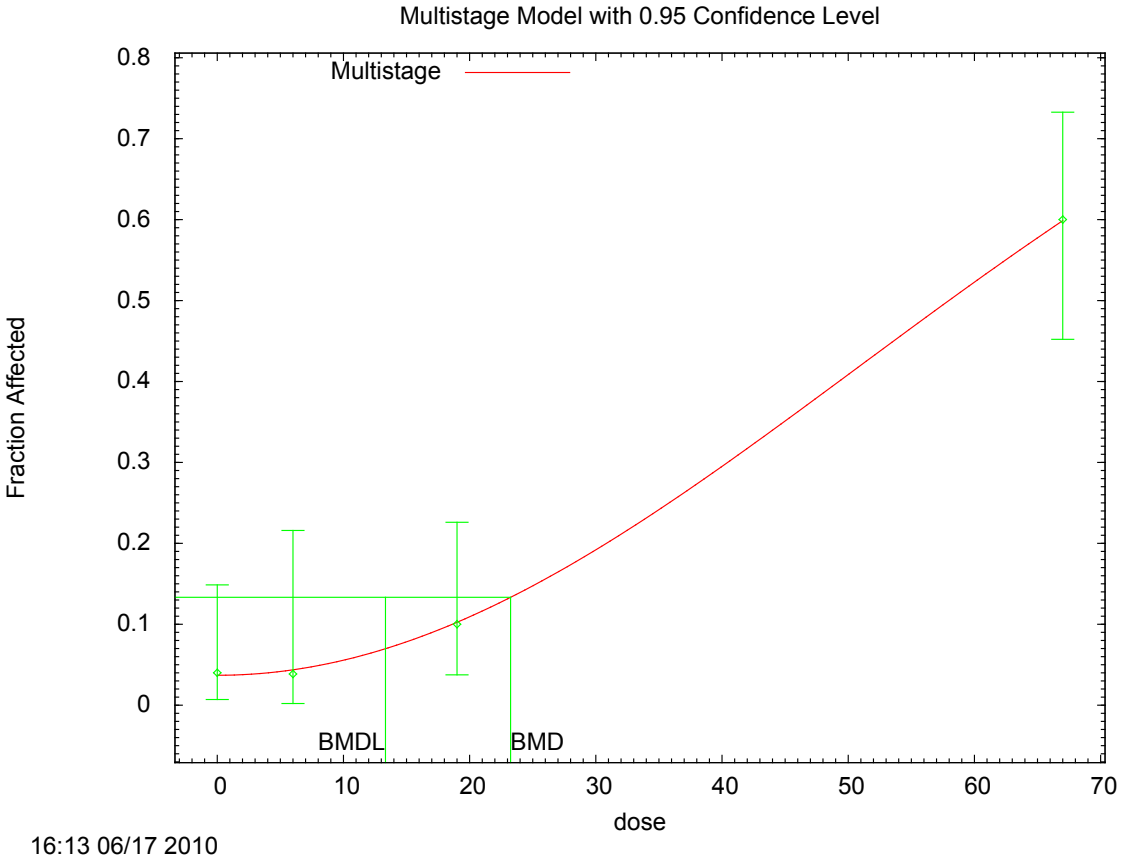
[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.
[e]Best-fitting model. Among models with adequate fit, the model with the lowest AIC was selected (Multistage 2-degree model).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD

Source: Moore 1994a

In accordance with the selection criteria mentioned above, the Multistage (2-degree) model was selected for MRL derivation. The dose-response curve is shown in Figure A-2.

**Figure A-2. Fit of Multistage (2-degree) Model to Data on 1,2,4-Trichlorobenzene, Incidence of Hepatocellular Hypertrophy in Male Rats**




Source: Moore 1994a

This page is intentionally blank.

# 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**

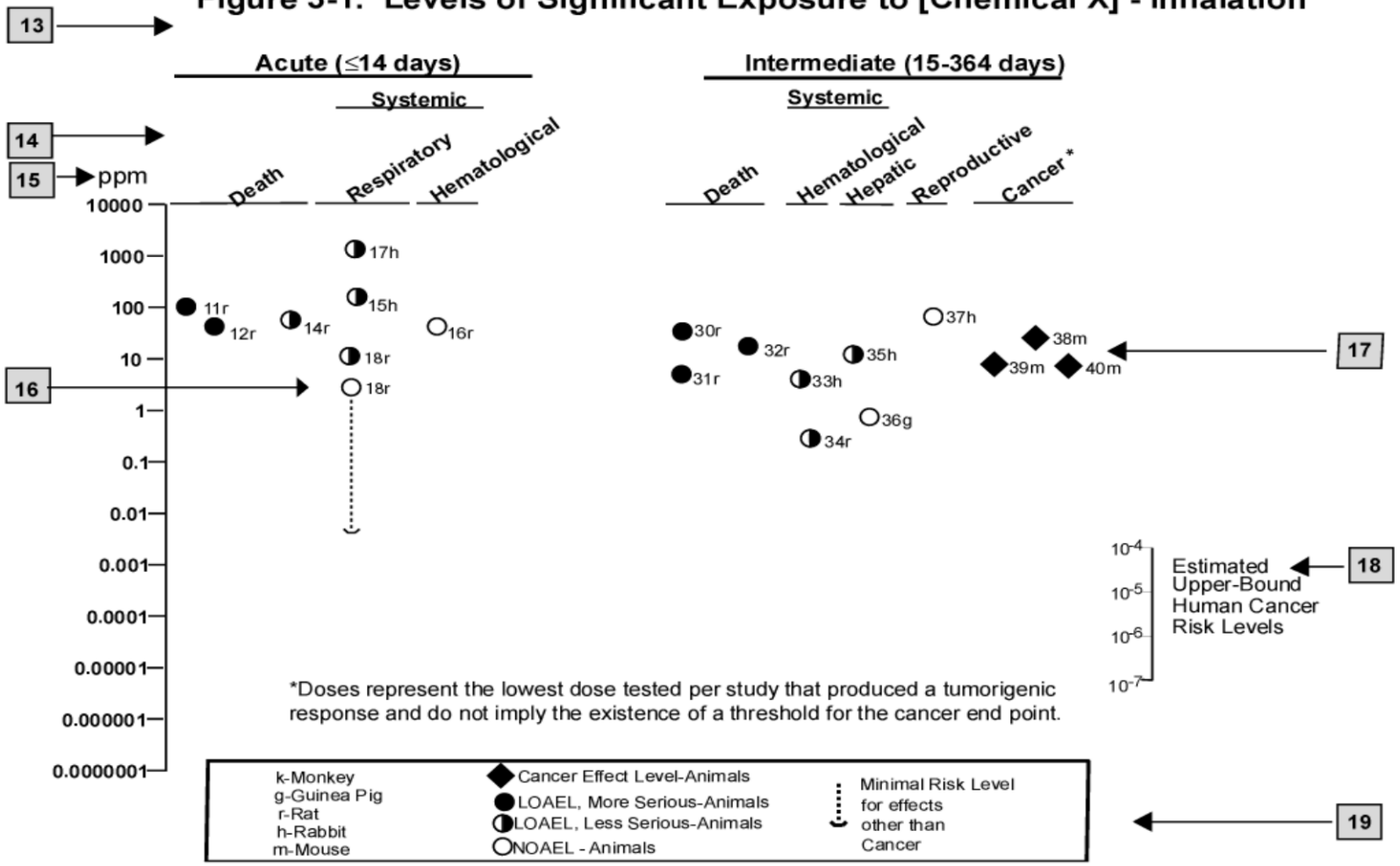
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

| Key to figure[a] | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) Less serious (ppm) | LOAEL (effect) Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| 2 → INTERMEDIATE EXPOSURE | | | | | | | |
| | 5 | 6 | 7 | 8 | 9 | | 10 |
| 3 → Systemic | ↓ | ↓ | ↓ | ↓ | ↓ | | ↓ |
| 18 | Rat | 13 wk 5 d/wk 6 hr/d | Resp | 3[b] | 10 (hyperplasia) | | Nitschke et al. 1981 |
| 4 → 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



This page is intentionally blank.

# 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 |

This page is intentionally blank.

# APPENDIX D. INDEX