

## APPENDIX A

## MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: **HMX**  
CAS Number: 2691-41-0  
Date: June 6, 1997  
Profile Status: Final (Post-Public Comment)  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 13  
Species: Mouse

Minimal Risk Level:

0.1  mg/kg/day  ppm

Reference:

Army. 1985d. HMX: 14-day toxicity study in mice by dietary administration. Ft. Detrick, MD: Research and Development Command, U.S. Army Medical Bioengineering Research and Development Laboratory. AD-A171 597 (authored by Greenough RJ, McDonald P).

Experimental design:

Groups of 6 male and 6 female B6C3F1 mice were administered HMX in the feed for 14 days at the following doses: 0, 100, 300, 900, and 2700 mg/kg/day for males; and 0, 320, 800, 2000, and 5000 mg/kg/day for females.

Effects noted in study and corresponding doses:

HMX-treated animals exhibited hyperkinesia when aroused at doses of 100 mg/kg/day. Convulsions were observed in two males exposed to 300 mg/kg/day. Other effects including piloerection, hunched posture, and increased sensitivity to auditory stimuli were also noted in animals exposed to this dose. No mention was made by the authors whether or not convulsions were observed in animals given higher doses. Necropsy of the brain did not reveal any abnormalities.

Dose and end point used for MRL derivation: 100 mg/kg/day hyperkinesia

NOAEL  LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? If so explain:

NA

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

NA

MRL Calculation:

LOAEL: 100 mg/kg/day

$MRL = LOAEL/UF = 100/1000 = 0.1 \text{ mg/kg/day}$

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CAS Number: 2691-41-0  
Date: June 6, 1997  
Profile Status: Final (Post-Public Comment)  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Graph Key: 16  
Species: Rat

Minimal Risk Level:

0.05  mg/kg/day  ppm

Reference:

Army. 1985c. HMX: 13 week toxicity study in rats by dietary administration. Ft. Detrick, MD: US. Army Medical Research and Development Command, U.S. Army Medical Bioengineering Research and Development Laboratory. (authored by Everett et al.)

Experimental design:

Groups of 20 male and 20 female Fischer rats were administered HMX in the feed for 13 weeks at the following doses: 0, 50, 150, 450, 1,350, and 4,000 mg/kg/day for males; 0, 50, 115, 270, 620, and 1,500 mg/kg/day for females.

Effects noted in study and corresponding doses:

A NOAEL was established for hepatic effects at 50 mg/kg/day. Hepatic effects including enlarged centrilobular cells with pale nuclei and dark cytoplasm were observed in males exposed to 150 mg/kg/day or more. In females administered 270 mg/kg/day or more, focal atrophy of the kidney tubules and dilatation was observed. Only high-dose animals (1,500 mg/kg/day for females, 4,000 mg/kg/day for males) were evaluated for serum chemistry parameters. Decreases in hemoglobin, packed cell volume, and blood urea nitrogen, and an increase in methemoglobin were observed in both males and females, although the elevation in methemoglobin levels was significant in males only. In addition, urinary pH was decreased while urinary volume was increased in females administered the highest dose. Crystals were observed in the urine of males administered the highest dose. Significant body weights were decreased in a dose-dependent manner, and many organ weights (adrenal, brain, heart, kidney, spleen, liver, lungs, and ovaries) were affected in a dose-dependent manner, however, the dose at which these changes became significant could not be determined. Histological effects were seen only in the liver and the kidneys. The results of this study indicate the liver and the kidneys as target organs. Ophthalmoscopic examination did not reveal any significant effects on the eyes that could be attributed to HMX treatment. Food intake did not show a consistent dose-related trend, but was reduced in treated animals as compared to controls.

Dose and end point used for MRL derivation: 50 mg/kg/day- Hepatic

NOAEL  LOAEL

Uncertainty factors used in MRL derivation:

- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Modifying factors used in MRL derivation:

- [X] 10 for use of a “limited database” and of data indicating that mice may be more sensitive than rats

Supporting studies:

Hepatocyte hyperplasia and cytoplasmic eosinophilia were noted in rats and mice exposed to 1,280 and 300 mg/kg/day HMX, respectively, for 14 days (Army 1985d, 1985e). No hepatic effects were observed in mice exposed to 90 mg/kg/day HMX (Army 1985b).

Was a conversion used from ppm in food or water to a mg/body weight dose? If so explain:

NA

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

NA

MRL Calculation:

NOAEL: 50 mg/kg/day

MRL = (NOAEL/UF)/ MF = (50/100)/10 = 0.05 mg/kg/day



## 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

##### Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upperbound 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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

#### LEGEND

##### See LSE Table 2-1

- (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. When sufficient data exists, 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2 “18r” data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.5, “Relevance to Public Health,” covers the relevance of animal data to human toxicity and Section 2.3, “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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (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 Lowest-Observed-Adverse-Effect Level (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 8 of the profile.
- (11) CEL A Cancer Effect Level (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.

## APPENDIX B

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

**LEGEND****See Figure 2-1**

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 intermediate and chronic 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<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 →

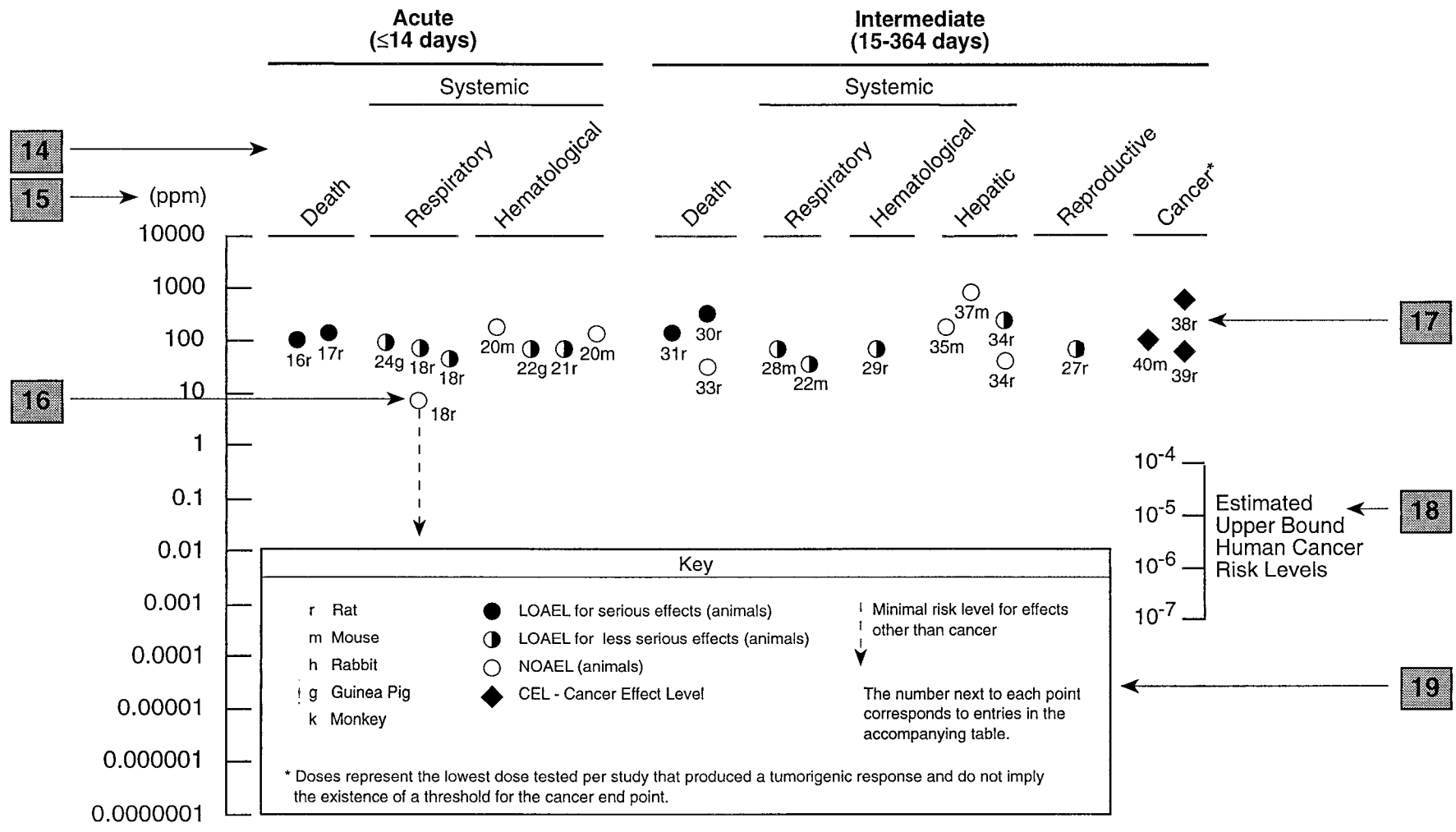
<sup>a</sup> The number corresponds to entries in Figure 2-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  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).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

# SAMPLE

13 → Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation



APPENDIX B

## Chapter 2 (Section 2.5)

### Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They 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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.7, "Interactions with Other Substances," and 2.8, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs). 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 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 LSE Tables.

## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

|                 |   |
|-----------------|---|
| ACGIH           | American Conference of Governmental Industrial Hygienists             |
| ADME            | Absorption, Distribution, Metabolism, and Excretion                   |
| AML             | acute myeloid leukemia  |
| atm             | atmosphere  |
| ATSDR           | Agency for Toxic Substances and Disease Registry                      |
| BCF             | bioconcentration factor   |
| BEI             | Biological Exposure Index   |
| BSC             | Board of Scientific Counselors  |
| C               | Centigrade  |
| CDC             | Centers for Disease Control   |
| CEL             | Cancer Effect Level   |
| CERCLA          | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR             | Code of Federal Regulations   |
| Ci              | curie   |
| CLP             | Contract Laboratory Program   |
| cm              | centimeter  |
| CML             | chronic myeloid leukemia  |
| CNS             | central nervous system  |
| d               | day   |
| DHEW            | Department of Health, Education, and Welfare                          |
| DHHS            | Department of Health and Human Services                               |
| DOL             | Department of Labor   |
| ECG             | electrocardiogram   |
| EEG             | electroencephalogram  |
| EPA             | Environmental Protection Agency                                       |
| EKG             | see ECG   |
| F               | Fahrenheit  |
| F <sub>1</sub>  | first filial generation   |
| FAO             | Food and Agricultural Organization of the United Nations              |
| FEMA            | Federal Emergency Management Agency                                   |
| FIFRA           | Federal Insecticide, Fungicide, and Rodenticide Act                   |
| fpm             | feet per minute   |
| ft              | foot  |
| FR              | <i>Federal Register</i>   |
| g               | gram  |
| GC              | gas chromatography  |
| gen             | generation  |
| HPLC            | high-performance liquid chromatography                                |
| hr              | hour  |
| IDLH            | Immediately Dangerous to Life and Health                              |
| IARC            | International Agency for Research on Cancer                           |
| ILO             | International Labor Organization                                      |
| in              | inch  |
| K <sub>d</sub>  | adsorption ratio  |
| kg              | kilogram  |
| kgg             | metric ton  |
| K <sub>oc</sub> | organic carbon partition coefficient                                  |

## APPENDIX C

|                  |   |
|------------------|---|
| K <sub>ow</sub>  | octanol-water partition coefficient                   |
| L                | liter   |
| LC               | liquid chromatography                                 |
| LC <sub>Lo</sub> | lethal concentration, low                             |
| LC <sub>50</sub> | lethal concentration, 50% kill                        |
| LD <sub>Lo</sub> | lethal dose, low                                      |
| LD <sub>50</sub> | lethal dose, 50% kill                                 |
| LOAEL            | lowest-observed-adverse-effect level                  |
| LSE              | Levels of Significant Exposure                        |
| m                | meter   |
| MA               | <u>trans,trans</u> -muconic acid                      |
| mCi              | millicurie  |
| mg               | milligram   |
| min              | minute  |
| mL               | milliliter  |
| mm               | millimeter  |
| mm Hg            | millimeters of mercury                                |
| mmol             | millimole   |
| mo               | month   |
| mppcf            | millions of particles per cubic foot                  |
| MRL              | Minimal Risk Level                                    |
| MS               | mass spectrometry                                     |
| NCE              | normochromatic erythrocytes                           |
| NIEHS            | National Institute of Environmental Health Sciences   |
| NIOSH            | National Institute for Occupational Safety and Health |
| NIOSHTIC         | NIOSH's Computerized Information Retrieval System     |
| ng               | nanogram  |
| nm               | nanometer   |
| NHANES           | National Health and Nutrition Examination Survey      |
| nmol             | nanomole  |
| NOAEL            | no-observed-adverse-effect level                      |
| NOES             | National Occupational Exposure Survey                 |
| NOHS             | National Occupational Hazard Survey                   |
| NPL              | National Priorities List                              |
| NRC              | National Research Council                             |
| NTIS             | National Technical Information Service                |
| NTP              | National Toxicology Program                           |
| OSHA             | Occupational Safety and Health Administration         |
| PEL              | permissible exposure limit                            |
| PCE              | polychromatic erythrocytes                            |
| pg               | picogram  |
| pmol             | picomole  |
| PHS              | Public Health Service                                 |
| PMR              | proportionate mortality ratio                         |
| ppb              | parts per billion                                     |
| ppm              | parts per million                                     |
| ppt              | parts per trillion                                    |
| REL              | recommended exposure limit                            |
| RfD              | Reference Dose  |
| RTECS            | Registry of Toxic Effects of Chemical Substances      |
| sec              | second  |

## APPENDIX C

|        |   |
|--------|---|
| SCE    | sister chromatid exchange                       |
| SIC    | Standard Industrial Classification              |
| SMR    | standard mortality ratio                        |
| STEL   | short term exposure limit                       |
| STORET | STORAGE and RETRIEVAL                           |
| TLV    | threshold limit value                           |
| TSCA   | Toxic Substances Control Act                    |
| TRI    | Toxics Release Inventory                        |
| TWA    | time-weighted average                           |
| UMDNJ  | University of Medicine and Dentistry New Jersey |
| U.S.   | United States                                   |
| UF     | uncertainty factor                              |
| yr     | year  |
| WHO    | World Health Organization                       |
| wk     | week  |
| >      | greater than                                    |
| ≥      | greater than or equal to                        |
| =      | equal to  |
| ≈      | approximately equal to                          |
| <      | less than                                       |
| ≤      | less than or equal to                           |
| %      | percent   |
| α      | alpha   |
| β      | beta  |
| δ      | delta   |
| γ      | gamma   |
| μm     | micrometer                                      |
| μg     | microgram                                       |

