APPENDIX A

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 endpoints, 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 2.3, “Relevance to Public Health,” covers the relevance of animal data to human toxicity and Section 2.4, “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 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 toxaphene 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 endpoint 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.

(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/m³ or ppm and oral exposure is reported in mg/kg/day.

(16) **NOAEL** In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates 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 (q1*).

(19) **Key to LSE Figure** The Key explains the abbreviations and symbols used in the figure.
### TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Species</th>
<th>Exposure frequency/duration</th>
<th>System</th>
<th>NOAEL (ppm)</th>
<th>LOAEL (effect)</th>
<th>Less serious (ppm)</th>
<th>Serious (ppm)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERMEDIATE EXPOSURE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>6</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Rat</td>
<td>5</td>
<td>13 wk</td>
<td>Resp</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
<td></td>
<td></td>
<td>Nitschke et al. 1981</td>
</tr>
</tbody>
</table>

**CHRONIC EXPOSURE**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>38</th>
<th>Rat</th>
<th>18 mo</th>
<th>20</th>
<th>(CEL, multiple organs)</th>
<th></th>
<th></th>
<th>Wong et al. 1982</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 Rat</td>
<td>5</td>
<td>89–104 wk</td>
<td>5d/wk</td>
<td>10 (CEL, lung tumors, nasal tumors)</td>
<td></td>
<td></td>
<td>NTP 1982</td>
<td></td>
</tr>
<tr>
<td>40 Mouse</td>
<td>6</td>
<td>79–103 wk</td>
<td>5d/wk</td>
<td>10 (CEL, lung tumors, hemangiosarcomas)</td>
<td></td>
<td></td>
<td>NTP 1982</td>
<td></td>
</tr>
</tbody>
</table>

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

<sup>o</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10<sup>3</sup> 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)
Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation

**Acute**
- Death
- Respiratory
- Hematological

**Intermediate**
- Death
- Respiratory
- Hematological
- Hepatic
- Reproductive
- Cancer

**Key**
- r: Rat
- m: Mouse
- h: Rabbit
- g: Guinea Pig
- k: Monkey
- • LOAEL for serious effects (animals)
- ○ LOAEL for less serious effects (animals)
- O NOAEL (animals)
- ◇ CEL - Cancer Effect Level
- † Minimal risk level for effects other than cancer

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
Chapter 2 (Section 2.4)

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 endpoints 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 endpoints 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 endpoints (if derived) and the endpoints 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 endpoint 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 endpoint 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 B
ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH American Conference of Governmental Industrial Hygienists
ADME Absorption, Distribution, Metabolism, and Excretion
atm atmosphere
ATSDR Agency for Toxic Substances and Disease Registry
BCF bioconcentration factor
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
CLP Contract Laboratory Program
cm centimeter
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
F₁ 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 Federal Register
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
Kd adsorption ratio
kg kilogram
kkg metric ton
Kₜ₀ organic carbon partition coefficient
Kₒₒ∕w octanol-water partition coefficient
L                      liter
LC                      liquid chromatography
LC_lo                     lethal concentration, low
LC_50                  lethal concentration, 50% kill
LD_lo                     lethal dose, low
LD_50                    lethal dose, 50% kill
LOAEL                      lowest-observed-adverse-effect level
LSE                      Levels of Significant Exposure
m                       meter
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
NIEHS                   National Institute of Environmental Health Sciences
NIOSH                  National Institute for Occupational Safety and Health
NIOSHITIC            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
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
SCE                        sister chromatid exchange
SIC                   Standard Industrial Classification
SMR                      standard mortality ratio
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>STEL</td>
<td>short term exposure limit</td>
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<td>STORET</td>
<td>STORAGE and RETRIEVAL</td>
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<td>TLV</td>
<td>threshold limit value</td>
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<td>TSCA</td>
<td>Toxic Substances Control Act</td>
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<td>TRI</td>
<td>Toxics Release Inventory</td>
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<td>TWA</td>
<td>time-weighted average</td>
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<td>U.S.</td>
<td>United States</td>
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<tr>
<td>UF</td>
<td>uncertainty factor</td>
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