APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Super-fund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the US. 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 a hundredfold 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, expert panel peer reviews, and agencywide 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.
**MINIMAL RISK LEVEL WORKSHEET**

Chemical Name: Diisopropyl Methylphosphonate  
CAS Number: 144-75-6  
Date: March 1998  
Profile Status: Draft 2 - Postpublic Comment  
Route: [ ] Inhalation [X] Oral  
Duration: [ ] Acute [X] Intermediate [ ] Chronic  
Graph Key: 27  
Species: Dog

**Minimal Risk Level:** 0.8 mg/kg/day

**Reference:** Hart 1980

**Experimental design:** Purebred beagles, four males and four females, received diisopropyl methylphosphonate in the diet at concentrations of 150, 1,500, and 3,000 ppm (4, 38, or 75 mg/kg/day) for 90 days. A control group of four males and four females was also maintained. At the outset of the study and at 48, and 13 weeks, hemograms and clinical chemistry parameters were determined for all of the dogs. The dogs were examined daily for general condition. Food consumption and body weights were determined weekly. At the termination of the 90-day study each dog was necropsied and selected tissues preserved and examined for histopathological changes.

**Effects noted in study and corresponding doses:**

The dogs appeared in good condition throughout the study. No hematological effects were ascribed to diisopropyl methylphosphonate. The authors concluded that the ingestion of diisopropyl methylphosphonate produced no toxic effects at the concentrations that the dogs received over the 90-day period of the study.

At the termination of the study a gross necropsy was performed on all of the dogs and no meaningful changes were observed. In addition, the liver, brain, thyroid, kidneys, adrenal glands, testes, ovaries, heart, and spleen were removed and weighed. No significant weight changes were noted. The liver, brain, thyroid, kidneys, adrenal glands, testes, ovaries, heart, spleen, spinal cord, lungs, pancreas stomach, small intestines, colon, urinary bladder, prostate, eyes with optic nerve, pituitary, marrow of the femur, rib junction, mesenteric lymph node, mammary tissue, skin, sciatic nerve, muscle, uterus, gall bladder, and any gross lesion of the 3000 ppm group and the control group were examined histologically and no clear or meaningful changes were noted.

**Dose and endpoint used for MRL derivation:**

[X] NOAEL [ ] LOAEL

75 mg/kg/day (3,000 ppm dietary concentration)
Uncertainty Factors used in MRL derivation:

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

\[ 75 \text{ mg/kg/day} \div 100 = 0.75 \text{ mg/kg/day} \]

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

The doses of diisopropyl methylphosphonate that the dogs received in the diet (1.50, 1,500, and 3,000 ppm) were calculated using the recommended reference value of 0.025 kg food/kg body weight/day as follows:

\[ (3,000 \text{ ppm}) \times (0.025 \text{ kg/kg/day}) = 75 \text{ mg/kg/day} \]

Other additional studies or pertinent information which lend support to this MRL:

Although this study (Hart 1980) did not identify an effect level, the NOAEL in this study is below the lowest-Observable-effect level (LOAEL) found in all studies examining the toxicity of diisopropyl methylphosphonate. The LOAEL for diisopropyl methylphosphonate is 345 mg/kg/day for male mink, and 455 mg/kg/day for female mink (average 400 mg/kg/day), doses at which statistically significant decreases in plasma (butyrylcholinesterase) but not RBC cholinesterase (acetylcholinesterase) activity was observed (Bucci et al. 1994). No effects were observed at 63 mg/kg/day in males and 82 mg/kg/day in females (average 73 mg/kg/day). A decrease in plasma cholinesterase activity is considered to be a marker of exposure rather than a marker of effect, while decreases in RBC acetylcholinesterase activity is thought to reflect decreases in brain acetylcholinesterase activity and is considered adverse.

Adverse effects, shortened RBC survival, increased Heinz body formation, increased number of reticulocytes, and reduced blood cell counts were observed at 747 mg/kg/day in males and 907 mg/kg/day in females (average 827 mg/kg/day). Although not statistically significant, the number of Heinz bodies was increased relative to controls at 400 mg/kg/day. The observed effects are consistent with a direct effect on RBC decreasing survival of the cells.

Metabolism studies in mink (Bucci et al. 1992) indicate that diisopropyl methylphosphonate is readily absorbed, metabolized to isopropylmethyl phosphonate, and excreted in the urine. After comparison with a metabolism study in dogs (Hart 1976), Bucci et al. (1992) concluded that mink handled the compound in a similar manner to dogs providing support for the use of mink when estimating risk to humans following diisopropyl methylphosphonate exposure. The metabolism study in mink (Bucci et al. 1992) suggested that at high doses (≥270 mg/kg) the principal pathway of metabolism of diisopropyl methylphosphonate is saturable. In the metabolism study the animals were treated by gavage; therefore, the dose rates in the gavage and dietary dosing studies may not be directly comparable. Further metabolism studies using dietary treatment are required to determine if the metabolism of diisopropyl methylphosphonate was saturated at the high doses (≥827 mg/kg/day) at which adverse effects on RBC were observed.

The Environmental Protection Agency derived a reference dose (RfD) of 0.08 mg/kg/day based on the same NOAEL from the Hart (1980) study. The RfD, however, utilized an additional uncertainty factor of 10 to extrapolate to chronic exposure.
MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Diisopropyl Methylphosphonate  
CAS Number: 144-75-6  
Date: March 1998  
Profile Status: Draft 2 - Postpublic Comment  
Route: [ ] Inhalation [X] Oral  
Duration: [ ] Acute [ ] Intermediate [X] Chronic  
Graph Key: 45  
Species: Mink  

Minimal Risk Level: 0.6 mg/kg/day  


Experimental design: In a 2-generation reproductive study, Ranch Wild mink received 0, 16, 45, or 262 mg/kg/day (males) or 0, 20, 57, or 330 mg/kg/day (females) diisopropyl methylphosphonate in the diet. These dosages were calculated for F1 animals by the study authors using actual concentrations in the feed of 0, 168, 490, and 2,774 ppm diisopropyl methylphosphonate. F1 generation females were treated for up to 13 months, while other generations and F1 males were treated for up to 8 months. Two groups of control animals were used. Animals were observed twice/day for clinical signs and were weighed weekly. In addition to standard examinations of body and organ weights, hematology, clinical chemistry, parental animals from both generations and representative kits underwent gross histopathological examination, which included reproductive organs in males and gross lesions and developmental defects in the kits. Reproductive parameters examined were live kits/litter, litter weight at birth and 28 days, and sex ratio. Ovarian follicles were also counted in high-dose females.  

Effects noted in study and corresponding doses:  

No effects were observed in F1 females at 57 mg/kg/day that were attributable to diisopropyl methylphosphonate after 13 months of exposure. Although there was no significant difference in food consumption or body weight in either generation compared to controls, the F1 females consumed almost 50% more feed than the F0 females, but this may have resulted from feed wastage. There was no treatment related change in litter size, percentage live births, kit weight or sex distribution in either generation. However, at 330 mg/kg/day, Heinz body counts were increased in F1 females after 6 and 13 months and high-dose males of this generation had increased Heinz body counts. There was a 31% decrease in plasma cholinesterase in animals fed 330 mg/kg/day for 13 months, but this is not considered to be biologically significant. There was also a significant increase in ovarian follicles among animals at this concentration (the only level examined). However, because treated dams of both generations produced as many offspring as the control animals, the biological significance of these findings is unclear.  

This study is supported by intermediate-duration NOAELs for hematological effects of 75 mg/kg/day in dogs (Hart 1980) and 73 mg/kg/day in mink (Bucci et al. 1994). In the Bucci et al. (1997) mink study, the next highest level, 262 or 330 mg/kg/day, produced hematological changes that included increased Heinz body counts, reticulocytes, mean cell volume, and decreased red blood cell counts.
Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

57 mg/kg/day (490 ppm dietary concentration)

Uncertainty Factors used in MRL derivation:

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

57 mg/kg/day ÷ 100 = 0.57 mg/kg/day

Was a conversion used from ppm in food or water to a m&odv weight dose? If so, explain:

The doses were calculated by the study authors.

Other additional studies or pertinent information which lend support to this MRL:

The critical study identified a NOAEL that was accompanied by a LOAEL. This study is supported by intermediate-duration NOAELs for hematological effects of 75 mg/kg/day in a dog study (Hart 1980) and 73 mg/kg/day in a mink study (Bucci et al. 1994). In the Hart (1980) study, beagle dogs received 0, 4, 38, or 75 mg/kg/day diisopropyl methylphosphonate in the diet for 90 days. No toxic effects, including hematological effects, were noted over the study period. In the Bucci et al. (1997) 2-generation reproductive study in mink, animals were fed 0, 16, 45, or 262 mg/kg/day (males) or 0, 20, 57, or 330 mg/kg/day (females) diisopropyl methylphosphonate for up to 12 months. While no hematological effects were found at the low- or mid-dose in either sex, high-dose males had increased Heinz body counts and high-dose females had decreased RBC counts and increased MCV, reticulocytes, and Heinz bodies. No hematological changes were found in the F1 kits after 11 weeks, but F2 high-dose male F1 kits had significantly decreased RBC counts at 6 weeks of age. High-dose F0 females also had significant increases in absolute and relative spleen weight and spleen-to-brain weight ratio. There was a treatment-related hematopoietic cell proliferation apparent in the spleen of these animals; the spleen showed evidence of RBC replacement. The next highest level, 262 or 330 mg/kg/day in males and females, respectively, produced hematological changes that included increased Heinz body counts, reticulocytes, mean cell volume, and decreased red blood cell counts.
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 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 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-l).

(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 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.
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.

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.

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

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.

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 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).

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.

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*).

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>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>INTERMEDIATE EXPOSURE</td>
<td>3</td>
<td>Rat</td>
<td>13 wk 5d/wk 6hr/d</td>
<td>Resp</td>
<td>3 b</td>
<td>10 (hyperplasia)</td>
</tr>
</tbody>
</table>

#### CHRONIC EXPOSURE

<table>
<thead>
<tr>
<th>Cancer</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>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>Rat</td>
<td>18 mo 5d/wk 7hr/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Rat</td>
<td>89–104 wk 5d/wk 6hr/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk 5d/wk 6hr/d</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* The number corresponds to entries in Figure 2-1.

b an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).
Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation

**Acute** (≤14 days)                      **Intermediate** (15-364 days)

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Respiratory</th>
<th>Hematological</th>
<th>Death</th>
<th>Respiratory</th>
<th>Hematological</th>
<th>Hepatic</th>
<th>Reproductive</th>
<th>Cancer*</th>
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<tbody>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**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
- * 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.

Estimated Upper Bound Human Cancer Risk Levels

The number next to each point corresponds to entries in the accompanying table.

Note: Upper bound human cancer risk levels are based on the assumption that the risk of cancer is proportional to the dose of the chemical. This is an estimate and should be used with caution.
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 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 C

**ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism, and Excretion</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
</tr>
<tr>
<td>BCF</td>
<td>bioconcentration factor</td>
</tr>
<tr>
<td>BEI</td>
<td>Biological Exposure Index</td>
</tr>
<tr>
<td>BSC</td>
<td>Board of Scientific Counselors</td>
</tr>
<tr>
<td>C</td>
<td>Centigrade</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
</tr>
<tr>
<td>CEL</td>
<td>Cancer Effect Level</td>
</tr>
<tr>
<td>CERCLA</td>
<td>Comprehensive Environmental Response, Compensation, and Liability Act</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>Ci</td>
<td>curie</td>
</tr>
<tr>
<td>CLP</td>
<td>Contract Laboratory Program</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>d</td>
<td>day</td>
</tr>
<tr>
<td>DHEW</td>
<td>Department of Health, Education, and Welfare</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
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<tr>
<td>DOL</td>
<td>Department of Labor</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>EEG</td>
<td>electroencephalogram</td>
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<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
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<tr>
<td>EKG</td>
<td>see ECG</td>
</tr>
<tr>
<td>F</td>
<td>Fahrenheit</td>
</tr>
<tr>
<td>F₁</td>
<td>first filial generation</td>
</tr>
<tr>
<td>FAO</td>
<td>Food and Agricultural Organization of the United Nations</td>
</tr>
<tr>
<td>FEMA</td>
<td>Federal Emergency Management Agency</td>
</tr>
<tr>
<td>FIFRA</td>
<td>Federal Insecticide, Fungicide, and Rodenticide Act</td>
</tr>
<tr>
<td>fpsm</td>
<td>feet per minute</td>
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<td>FR</td>
<td><em>Federal Register</em></td>
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<td>g</td>
<td>gram</td>
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<td>GC</td>
<td>gas chromatography</td>
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<td>generation</td>
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<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
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<td>hour</td>
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<tr>
<td>IDLH</td>
<td>Immediately Dangerous to Life and Health</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>ILO</td>
<td>International Labor Organization</td>
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<tr>
<td>in</td>
<td>inch</td>
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<tr>
<td>Kd</td>
<td>adsorption ratio</td>
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</table>
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
STE L 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
\geq greater than or equal to
=  equal to
<  less than
\leq less than or equal to
%  percent
\alpha  alpha
\beta  beta
\delta  delta
\gamma  gamma
\mu m  micrometer
\mu g  microgram