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 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 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.
Chemical name: Chlorpyrifos
CAS number: 508 15-00-4
Date: August 1997
Profile status: Final Post-public Draft
Route: [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 5
Species: Human

MRL: 0.003 [X] mg/kg/day [ ] ppm [ ] mg/m³
Reference: Coulston et al. (1972)

Experimental design: 16 adult human male volunteers (4 per dose group) were treated with 0, 0.014, 0.03, or 0.10 mg/kg/day chlorpyrifos by capsule. Those subjects receiving 0.014 and 0.03 mg/kg/day were exposed for 20 days; those receiving 0.10 mg/kg/day were exposed for only 9 days.

Effects noted in study and corresponding doses: Those subjects receiving 0.10 mg/kg/day were exposed for only 9 days because of blurred vision and a runny nose in one of the subjects. Plasma cholinesterase was decreased approximately 65% compared to controls in that group. No effect on plasma cholinesterase was seen at the lower doses and erythrocyte cholinesterase was unaffected by any of the chlorpyrifos doses. Thus, the NOAEL for chlorpyrifos plasma cholinesterase inhibition was 0.03 mg/kg/day. Based on this NOAEL, an MRL of 0.003 mg/kg was calculated: 0.03 mg/kg divided by an uncertainty factor of 10 for human variability. Please note that the combination of length of exposure period and the critical effect in this study enable it to be used for the derivation of both acute- and intermediate-duration oral exposure MRLs.

\[
\text{MRL} = \frac{\text{Human dose}}{\text{Uncertainty factor}} = \frac{0.03 \text{ mg/kg}}{10} = 0.003 \text{ mg/kg}
\]

Dose endpoint used for MRL derivation: Plasma cholinesterase inhibition

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from num in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? No.

If so, explain:

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


The MRL study is further supported by a study by Deacon et al. (1980). Female CF-1 mice were exposed by gavage to 1, 10, or 2 mg/kg/day Dursban® (96.8% chlorpyrifos) as a solution in cottonseed oil on gestation day (Gd) 6, Gds 6-10, or Gds 6-15. Controls received cottonseed oil alone. Five hours after the final dosing (Gds 6, 10, or 15) blood was obtained via cardiac puncture and plasma and erythrocyte cholinesterase activities determined. Plasma and erythrocyte cholinesterase levels were significantly decreased from control values among mice given 10 or 25 mg/kg chlorpyrifos on day 6 (plasma, 95 and 97%, respectively; erythrocyte, 40 and 20%, respectively) and, days 6-10 (plasma, 97 and 99%, respectively; erythrocyte, 43 and 71%, respectively), or Gds 6-15 (plasma, 96 and 98%, respectively; erythrocyte, 43 and 57%, respectively). Plasma cholinesterase levels were significantly reduced among mice given 1 mg/kg chlorpyrifos during the same time intervals (69, 78, and 85%, respectively). Erythrocyte cholinesterase levels were also reduced (43%) after 1 mg/kg chlorpyrifos, but only after exposure on Gds 6-10. In a concurrent study, no effects on plasma or erythrocyte cholinesterase activity were observed at 0.1 mg/kg chlorpyrifos.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Chlorpyrifos
CAS number: 50815-00-4
Date: July 1997
Profile status: Final Post-public Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 15
Species: Human

MRL: 0.003 [X] mg/kg/day [ ] ppm [ ] mg/m³


Experimental design: 16 adult human male volunteers (4 per dose group) were treated with 0, 0.014, 0.03, or 0.10 mg/kg/day chlorpyrifos by capsule. Those subjects receiving 0.014 and 0.03 mg/kg/day were exposed for 20 days; those receiving 0.10 mg/kg/day were exposed for only 9 days.

Effects noted in study and corresponding doses: Those subjects receiving 0.10 mg/kg/day were exposed for only 9 days because of blurred vision and a runny nose in one of the subjects. Plasma cholinesterase was decreased approximately 65% compared to controls in that group. No effect on plasma cholinesterase was seen at the lower doses and erythrocyte cholinesterase was unaffected by any of the chlorpyrifos doses. Thus, the NOAEL for chlorpyrifos plasma cholinesterase inhibition was 0.03 mg/kg/day.

Based on this NOAEL, an MRL of 0.003 mg/kg was calculated: 0.03 mg/kg divided by an uncertainty factor of 10 for human variability. Please note that the combination of length of exposure period and the critical effect in this study enable it to be used for the derivation of both acute- and intermediate-duration oral exposure MRLs.

MRL = Human dose ÷ Uncertainty factor

\[
\begin{align*}
&= 0.03 \text{ mg/kg} \times \frac{1}{10} \\
&= 0.003 \text{ mg/kg/day}
\end{align*}
\]

Dose endpoint used for MRL derivation: Plasma cholinesterase inhibition

[X] NOAEL [ ] LOAEL
Uncertainty factors used in MRL derivation:
[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:
APPENDIX A

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

Was a conversion used from intermittent to continuous exposure? No.
If so, explain:

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


The MRL study is further supported by a study by Deacon et al. (1980). Female CF-1 mice were exposed by gavage to 1, 10, or 2 mg/kg/day Dursban F® (96.8% chlorpyrifos) as a solution in cottonseed oil on Gds 6, 6-10, or 6-15. Controls received cottonseed oil alone. Five hours after the final dosing (Gds 6, 10, or 15), blood was obtained via cardiac puncture and plasma and erythrocyte cholinesterase activities determined. Plasma and erythrocyte cholinesterase levels were significantly decreased from control values among mice given 10 or 25 mg/kg chlorpyrifos on day 6 (plasma, 95 and 97%, respectively; erythrocyte, 40 and 20%, respectively) and, days 6-10 (plasma, 97 and 99%, respectively; erythrocyte, 43 and 71%, respectively), or Gds 6-15 (plasma, 96 and 98%, respectively; erythrocyte, 43 and 57%, respectively). Plasma cholinesterase levels were significantly reduced among mice given 1 mg/kg chlorpyrifos during the same time intervals (69, 78, and 85%, respectively). Erythrocyte cholinesterase levels were also reduced (43%) after 1 mg/kg chlorpyrifos, but only after exposure on Gds 6-10. In a concurrent study, no effects on plasma or erythrocyte cholinesterase activity were observed at 0.1 mg/kg chlorpyrifos.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Chlorpyrifos  
CAS number: 50815-00-4  
Date: July 1997  
Profile status: Final Post-public Draft  
Route: [X] Oral  
Duration: [X] Chronic  
Key to figure: 42  
Species: Rat  
MRL: 0.001 [X] mg/kg/day [ ] ppm [ ] mg/m³  
Reference: McCollister et al. 1974  

Experimental design: Sherman rats (25 males and 25 females) were dose fed chlorpyrifos at 0, 0.01, 0.03, 0.1, 1, or 3 mg/kg/day for 2 years beginning at 7-weeks of age. Additional groups of 5-7 rats of each sex at each dose level were set up to provide interim pathological examination and cholinesterase (ChE) determinations. Clinical observations, body weights, food consumption and mortality were monitored. At 6-month intervals, blood and urine samples were collected from selected rats receiving 0, 1, or 3 mg/kg/day. The packed cell volume, hemoglobin, erythrocyte count and total and differential leucocyte counts were determined in the blood. Urine was analyzed for total solids, pH, albumin, sugar, occult blood and ketones. The ChE activity of the plasma and red blood cells (RBC) was determined for all rats in the groups that were killed after receiving the test diets for 1 week, and 1, 3, 6, 9, 12, and 18 months, as well as for selected rats from those given each dose for 2 years. Brain ChE was measured in rats killed at 6, 12, 18, and 24 months. To characterize the recovery of the ChE activity in plasma, red cells and brain, some rats were maintained on the various diets containing chlorpyrifos for 12 months, and subsequently on the control diet for 7-8 weeks prior to sacrifice. Blood urea nitrogen (BUN), serum alkaline phosphatase (AP) and serum glutamic-pyruvic transaminase (SGPT) were determined on blood samples collected from rats killed at 12, 18, and 24 months. Necropsies were conducted on all rats killed at 12, 18, and 24 months and on those that received control feed for 7-8 weeks after having received chlorpyrifos diets for 12 months. These rats were fasted for 16 hours, decapitated, and weighed. The brain, heart, liver, kidney, spleen, and testes were removed and weighed. Portions of these tissues were preserved in 10% formalin, and histopathological examinations were performed on these tissues, as well as eye, pituitary, thyroid, and parathyroid glands, trachea, esophagus, lungs, aorta, stomach, pancreas, small intestine, colon, mesenteric lymph nodes, urinary bladder, accessory sex glands, ovaries, uterus, skeletal muscle, sciatic nerve, spinal cord, sternum, sternal bone marrow, adrenal gland, and any nodules or masses suggestive of tumor development or other pathological processes. Histopathological examinations were also conducted on the tissues of all rats exhibiting grossly visible nodules or masses, and on those killed in a moribund state or that died spontaneously, unless this was precluded by autolysis.

Effects noted in study and corresponding doses: Clinical observations did not detect evidence of a cholinergic overstimulation or any other compound-related effect. Brain cholinesterase (ChE) activity in both male and female rats displayed an overall reduction of 56% in rats fed 3 mg/kg/day chlorpyrifos during the 2-year study. No overall effect on brain ChE was observed at the lower doses. Plasma and RBC ChE activity were depressed for both male and female rats dosed with diets containing 1 or 3 mg/kg/day chlorpyrifos. At 1 mg/kg/day chlorpyrifos, plasma ChE was depressed.
20-53%; RBC ChE activity was decreased 65-70% at that dose. Doses of 0.1 mg/kg/day and below had no effect on either plasma or RBC activity. Cholinesterase activities in plasma, RBC, and brain of rats fed chlorpyrifos-containing diets for 1 year returned to normal levels after switching to a control diet for 7-8 weeks. There was no effect of treatment on organ weights, histopathology, or number and types of tumors. It was concluded that 0.1 mg chlorpyrifos/kg/day fed in the diet for 2 years produced no significant toxicological effect in rats.

MRL = Human dose + Uncertainty factor (UF = 10 for extrapolation from animal data; UF = 10 for human variability)

\[
= 0.1 \text{ mg/kg/day} \times \frac{1}{10} \times \frac{1}{10} \\
= 0.001 \text{ mg/kg/day}
\]

Dose endpoint used for MRL derivation: Acetylcholinesterase inhibition

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

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

Was a conversion used from intermittent to continuous exposure? No.
If so, explain:

Other additional studies or pertinent information that lend support to this MRL: No.

Agency Contact (Chemical Manager): John F. Risher, Ph.D.
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 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 datapoints 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 2.4, “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 Frequecy/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 (q*).

(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&lt;sup&gt;a&lt;/sup&gt;</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>2</td>
<td>Systemic</td>
<td>13 wk</td>
<td>Resp</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
<td></td>
<td></td>
<td>Nitschke et al. 1981</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d/wk / 6hr/d</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Rat</td>
<td>13 wk</td>
<td>Resp</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
<td></td>
<td></td>
<td>Nitschke et al. 1981</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d/wk / 6hr/d</td>
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<td></td>
</tr>
<tr>
<td>CHRONIC EXPOSURE</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Rat</td>
<td>18 mo</td>
<td></td>
<td>20</td>
<td>(CEL, multiple organs)</td>
<td></td>
<td></td>
<td>Wong et al. 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d/wk / 7hr/d</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>39</td>
<td>Rat</td>
<td>89–104 wk</td>
<td></td>
<td>10</td>
<td>(CEL, lung tumors, nasal tumors)</td>
<td></td>
<td></td>
<td>NTP 1982</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5d/wk / 6hr/d</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk</td>
<td></td>
<td>10</td>
<td>(CEL, lung tumors, hemangiosarcomas)</td>
<td></td>
<td></td>
<td>NTP 1982</td>
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<tr>
<td></td>
<td></td>
<td>5d/wk / 6hr/d</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<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 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). 
## TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

<table>
<thead>
<tr>
<th>Key to figure&lt;sup&gt;a&lt;/sup&gt;</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></td>
<td><strong>INTERMEDIATE EXPOSURE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10:</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Rat</td>
<td>13 wk</td>
<td>5d/wk</td>
<td>Resp</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6hr/d</td>
<td></td>
<td></td>
<td></td>
<td>Nitschke et al. 1981</td>
</tr>
</tbody>
</table>

**CHRONIC EXPOSURE**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Rat</th>
<th>18 mo</th>
<th>5d/wk</th>
<th>7hr/d</th>
<th>20</th>
<th>(CEL, multiple organs)</th>
<th>Wong et al. 1982</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>Rat</td>
<td>89–104 wk</td>
<td>5d/wk</td>
<td>6hr/d</td>
<td>10</td>
<td>(CEL, lung tumors, nasal tumors)</td>
<td>NTP 1982</td>
</tr>
<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk</td>
<td>5d/wk</td>
<td>6hr/d</td>
<td>10</td>
<td>(CEL, lung tumors, hemangiosarcomas)</td>
<td>NTP 1982</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> 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)
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 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “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>Abbreviation</th>
<th>Description</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>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>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>CLP</td>
<td>Contract Laboratory Program</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</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>
</tr>
<tr>
<td>DOL</td>
<td>Department of Labor</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
</tr>
<tr>
<td>EKG</td>
<td>see ECG</td>
</tr>
<tr>
<td>F</td>
<td>Fahrenheit</td>
</tr>
<tr>
<td>F&lt;sub&gt;1&lt;/sub&gt;</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>fpm</td>
<td>feet per minute</td>
</tr>
<tr>
<td>ft</td>
<td>foot</td>
</tr>
<tr>
<td>FR</td>
<td><em>Federal Register</em></td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>gen</td>
<td>generation</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<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>
</tr>
<tr>
<td>in</td>
<td>inch</td>
</tr>
<tr>
<td>Kd</td>
<td>adsorption ratio</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>kkg</td>
<td>metric ton</td>
</tr>
<tr>
<td>K&lt;sub&gt;oc&lt;/sub&gt;</td>
<td>organic carbon partition coefficient</td>
</tr>
<tr>
<td>K&lt;sub&gt;ow&lt;/sub&gt;</td>
<td>octanol-water partition coefficient</td>
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</tbody>
</table>
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
NIOSHIC  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
RTCECS  Registry of Toxic Effects of Chemical Substances
sec  second
SCE  sister chromatid exchange
SIC  Standard Industrial Classification
SMR  standard mortality ratio
APPENDIX C

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>STEL</td>
<td>short term exposure limit</td>
</tr>
<tr>
<td>STORET</td>
<td>STORAGE and RETRIEVAL</td>
</tr>
<tr>
<td>TLV</td>
<td>threshold limit value</td>
</tr>
<tr>
<td>TSCA</td>
<td>Toxic Substances Control Act</td>
</tr>
<tr>
<td>TRI</td>
<td>Toxics Release Inventory</td>
</tr>
<tr>
<td>TWA</td>
<td>time-weighted average</td>
</tr>
<tr>
<td>U.S.</td>
<td>United States</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
</tr>
<tr>
<td>yr</td>
<td>year</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wk</td>
<td>week</td>
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> 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 micron
\mu microgram