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.
### APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET(S)**

<table>
<thead>
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<th>Chemical name:</th>
<th>Methyl tert-butyl ether (MTBE)</th>
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<td>CAS number:</td>
<td>1634-04-43</td>
</tr>
<tr>
<td>Date:</td>
<td>July 1996</td>
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<tr>
<td>Profile status:</td>
<td>Third Post Public Comment Draft</td>
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<td>Route:</td>
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<td>Key to figure:</td>
<td>32</td>
</tr>
<tr>
<td>Species:</td>
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**MRL:** 2 [ ] mg/kg/day [X] ppm [ ] mg/m³

**Reference:** Gill 1989

**Experimental design** (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 22 male and 22 female Fischer 344 rats were exposed to 0, 800, 4,000, or 8,000 ppm MTBE for 6 hours. Groups of 14 rats/sex were studied for motor activity, and the remaining groups of 8 rats/sex were given a functional observation battery of tests at 1, 6, and 24 hours after exposure.

**Effects noted in study and corresponding doses:** Concentration-related increases in ataxia and duck-walk gait occurred in both males and females at 4,000 and 8,000 ppm. Other effects noted in high-dose males included labored respiration pattern, decreased muscle tone, decreased performance on a treadmill, and increased hind limb splay. Other effects noted in females included decreased hind limb grip strength at 24,000 ppm and labored respiration and increased latency to rotate on the inclined screen at 8,000 ppm. These effects were seen at 1 hour after exposure, but not at 6 or 24 hours after exposure, indicating the transient nature of the effect. Motor activity changes, for which the time course corresponded with the functional observation battery findings, supported the exposure-related central nervous system sedation. No neurological effects were observed at the NOAEL of 800 ppm for 6 hours.

**Dose endpoint used for MRL derivation:** 800 ppm, no central nervous system sedation

**[x] NOAEL [ ] LOAEL**

**Uncertainty factors used in MRL derivation:** 100

[ ] 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?**

If so, explain: No
If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL(HEC) was calculated for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1 was used for this ratio. Therefore, because the NOAEL in rats and the NOAEL(HEC) are the same, an uncertainty factor of 10, rather than 3, for extrapolation from animals to humans was recommended by the Interagency MRL Work Group.

Was a conversion used from intermittent to continuous exposure?
If so, explain: The NOAEL of 800 ppm was multiplied by 6 hour/24 hours to yield a NOAEL_{ADJ} of 200 ppm.

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

The NOAEL of 800 ppm is supported by another study, which found only increased motor activity in female rats, but no other neurological effects in rats at 800 ppm, 6 hours/day, 5 days/week for 13 weeks (Dodd and Kintigh 1989). In this study, hypoactivity at 4,000 ppm and hypoactivity and ataxia at 8,000 ppm were observed daily after the 6 hour/day exposure, thus representing effects of acute exposure. A number of acute-duration inhalation studies in rats, mice, and rabbits have described similar clinical signs of neurotoxicity at MTBE concentrations ≤ 2,000 ppm (ARCO 1980; Biodynamics 1981; Bioresearch Labs 1990d; Dodd and Kintigh 1989; Tyl and Neeper-Bradley 1989; Tyl 1989).

Agency Contact (Chemical Manager): Moiz Mumtaz
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Methyl tert-butyl ether (MTBE)
CAS number: 1634-04-4
Date: July 1996
Profile status: Third Post Public Comment Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Key to figure: 60
Species: Rat

MRL: 0.7 [ ] mg/kg/day [xl ppm [ ] mg/m³

Reference: Neep er-Bradley 1991

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 25 male and 25 female rats were exposed to 0, 400, 3,000, or 8,000 ppm MTBE for 6 hours/day, 5-7 days/week for 14-19 weeks in a reproductive study.

Effects noted in study and corresponding doses: Exposure for 10 weeks prior to mating and through day 19 of gestation to the concentration of 8,000 ppm MTBE resulted in salivation and hypoactivity in F0 and F1 parental rats. F0 and F1 parental groups also showed hypoactivity and lack of startle response, as well as blepharospasm, at 3,000 ppm.

Dose endpoint used for MRL derivation: 400 ppm, no central nervous system sedation

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation: 100

[ ] 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? If so, explain: No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL(HEC) was calculated for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1 is used for this ratio. Therefore, because the NOAEL in rats and the NOAEL(HEC) are the same, an uncertainty factor of 10, rather than 3, for extrapolation from animals to humans was recommended by the Interagency MRL Work Group.

Was a conversion used from intermittent to continuous exposure? If so, explain: The NOAEL of 400 ppm was multiplied by 6 hour/24 hours/day and by 5 days/7 days/week to yield a NOAELADJ of 71 ppm.
Other additional studies or pertinent information that lend support to this MRL:

In a 13-week study, rats were exposed to 0, 800, 4,000, or 8,000 ppm MTBE 6 hours/day, 5 days/week (Dodd and Kintigh 1989). At 4,000 ppm, the rats were hypoactive, had elevated body temperature, and decreased hind limb grip strength. At 8,000 ppm, both ataxia and hypoactivity were observed. Some hyperactivity occurred in female rats at 800 ppm, but no signs were observed in males at 800 ppm.

Agency Contact (Chemical Manager): Moiz Mumtaz
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Methyl tert-butyl ether (MTBE)
CAS number: 1634-04-4
Date: July 1996
Profile status: Third Post Public Comment Draft
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 70
Species: Rat

MRL: 0.7 [ ] mg/kg/day [x] ppm [ ] mg/m^3

Reference: Chun et al. 1992

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 50 male and 50 female Fischer 344 rats were exposed to 0, 400, 3,000, or 8,000 ppm MTBE 6 hours/day, 5 days/week for up to 24 months. Male rats exposed to 3,000 and 8,000 ppm had increased mortality and decreased mean survival time due to chronic progressive nephropathy and these groups were terminated at weeks 97 and 82, respectively. Endpoints monitored were clinical signs, body weight, organ weight, hematological parameters, corticosterone evaluation, and comprehensive gross and histological examination.

Effects noted in study and corresponding doses: Male rats exposed to ≥ 400 ppm had increased mortality and decreased mean survival time due to chronic progressive nephropathy. Increased absolute and relative liver and kidney weights were observed in females at ≥ 3,000 ppm. No gross or histopathological lesions were found in the liver of either sex, but concentration-related increased incidence and severity of chronic progressive nephropathy, accompanied by osteodystrophy, hyperplasia of the parathyroids, and mineralization in numerous tissues were found in males at all exposure levels and in females at ≥ 3,000 ppm. No evidence of renal effects was found in the female rats at 400 ppm.

Dose endpoint used for MRL derivation: 400 ppm, no increased incidence and severity of chronic progressive nephropathy.

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation: 100

[ ] 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?
If so, explain: No
APPENDIX A

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The NOAEL_{HEC} was calculated for a gas:extrarespiratory effect in rats assuming periodicity was attained. Because the b:a lambda values are unknown for the experimental species (a) and humans (h), a default value of 1 is used for this ratio. Therefore, because the NOAEL in rats and the NOAEL_{HEC} are the same, an uncertainty factor of 10, rather than 3, for extrapolation from animals to humans was recommended by the Interagency MRL Work Group.

Was a conversion used from intermittent to continuous exposure? If so, explain: The NOAEL was multiplied by 6 hour/24 hour/day and 5 days/7 days/week to yield a NOAEL_{ADJ} of 71 ppm

Other additional studies or pertinent information that lend support to this MRL:
The higher incidence and greater severity of chronic progressive nephropathy at lower exposure concentrations in male rats compared with female rats may be due to the exacerbation of this syndrome by the accumulation of α₂u-globulin. Because enhancement of chronic progressive nephropathy, which led to increased mortality and decreased survival time in males, is associated with α₂u-globulin accumulation in male rats only, these endpoints in male rats are not considered for MRL derivation. However, since female rats also had enhanced chronic progressive nephropathy not associated with α₂u-globulin accumulation, the chronic inhalation MRL of 2 ppm was calculated based on the NOAEL of 400 ppm for kidney effects in female rats. The chronic-duration inhalation NOAEL for renal effects is also a NOAEL for clinical signs of neurotoxicity in rats in this study. The NOAEL of 400 ppm for chronic-duration inhalation exposure to MTBE is supported by a similar study in male and female mice similarly exposed to same concentrations for 18 months (Burleigh-Flayer et al. 1992). In this study, absolute and relative liver weights were increased at ≥ 3,000 ppm and absolute and relative kidney weights were increased at 8,000 ppm. Comprehensive histological examination of organs and tissues revealed an increased incidence of hepatocellular hypertrophy and hepatocellular adenoma in female mice at 8,000 ppm. The NOAEL for liver effects in this study was 400 ppm, which was also a NOAEL for neurotoxicity in mice in this study.

Agency Contact (Chemical Manager): Moiz Mumtaz
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Methyl tert-butyl ether (MTBE)
CAS number: 1634-04-4
Date: July 1996
Profile status: Third Post Public Comment Draft
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Key to figure: 8
Species: Rat

MRL: 0.4 [x] mg/kg/day [ ] ppm [ ] mg/m³


Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 6 male and 6 female Fischer 344 rats were treated by gavage with MTBE in water at doses of 0, 40, and 400 mg/kg in this pharmacokinetic study.

Effects noted in study and corresponding doses: The rats given 400 mg/kg showed signs of drowsiness.

Dose endpoint used for MRL derivation: 40 mg/kg, no drowsiness

[x] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation: 100

[ ] 1 [ ] 3 [x] 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 body weight dose? If so, explain: No

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

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

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

Although this study was designed as a pharmacokinetic study rather than a toxicity study, the observation of drowsiness is consistent with observations of central nervous system sedation in animals exposed to MTBE by the inhalation and oral routes, and the study provides the highest NOAEL below which there is no LOAEL. In other acute-duration oral studies, rats had mild central nervous system depression at 1,900 mg/kg and ataxia at 2,450 mg/kg (ARCO 1990), salivation at 90 mg/kg and hypoactivity and/or ataxia at 440 mg/kg (ITT Research Institute 1992), and profound but transient anesthesia at 1,200 mg/kg or 1,428 mg/kg/day for 14 days (Robinson et al. 1990).

Agency Contact (Chemical Manager): Moiz Mumtaz
MINIMAL RISK LEVEL WORKSHEET

Chemical name: Methyl tert-butyl ether (MTBE)
CAS number: 1634-04-4
Date: July 1996
Profile status: Third Post Public Comment Draft
Route: Oral
Duration: Intermediate
Key to figure: 15
Species: Rat

MRL: 0.3 mg/kg/day [ ] ppm [ ] mg/m³

Reference: Robinson et al. 1990

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 10 male and 10 female Sprague-Dawley rats were treated by gavage with MTBE in corn oil at doses of 0, 100, 300, 900, and 1,200 mg/kg/day, 7 days/week for 90 days.

Effects noted in study and corresponding doses: Relative and absolute lung weights were significantly increased in males at 1,200 mg/kg/day. Treated rats in all dose groups had diarrhea throughout the exposure period. Heart weight was significantly increased in female rats at 900 mg/kg/day. In females at 1,200 mg/kg/day, erythrocyte counts, hemoglobin, and hematocrit values were significantly increased, while leukocyte counts were significantly decreased. In male rats at 1,200 mg/kg/day, mean corpuscular volume values were significantly decreased and monocyte values were significantly elevated. Significant increases in relative liver weights were found in females at 900 mg/kg/day and in males at 900 and 1,200 mg/kg/day. Serum lactic dehydrogenase levels were significantly elevated in females at 300 mg/kg/day, and serum aspartate aminotransferase levels were significantly elevated in males at 300 and 1,200 mg/kg/day. Blood urea nitrogen (BUN) levels were significantly decreased in males and females at all dose levels, i.e., at ≥100 mg/kg/day. No histopathological lesions were found in the liver. Relative kidney weights were significantly elevated in female rats at ≥300 mg/kg/day, and absolute and relative kidney weights were significantly elevated in males rats at ≥900 mg/kg/day. Significant microscopic changes were observed in kidneys from treated male rats. Tubular changes, which were more severe in the 1,200 mg/kg/day dose-group males compared with controls, consisted of mild increases in cytoplasmic hyaline droplets in proximal tubular cells and small numbers of intratubular granular casts at the junction of the outer and inner stripe of the outer medulla. Female rats given 1,200 mg/kg/day had significantly elevated adrenal gland weights. Final body weight in both males and females decreased in a dose-dependent manner compared with controls, but the decrease in final body weight was significant only in females at 1,200 mg/kg/day. Cholesterol was significantly elevated in all treated female rats and in 900 mg/kg/day males. Profound anesthesia was observed immediately following dosing with 1,200 mg/kg/day, but the rats recovered in approximately 2 hours.

Dose endpoint used for MRL derivation: Decreased BUN levels at 100 mg/kg/day

[ ] NOAEL [x] LOAEL
Uncertainty factors used in MRL derivation: 300

[ ] 1 [x] 3 [ ] 10 (for use of a minimal 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?
If so, explain: No

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

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

Other additional studies or pertinent information that lend support to this MRL:
Significantly decreased BUN levels were also observed in female rats given 1,428 mg/kg/day orally for 14 days (Robinson et al. 1990). In a 4-week study, groups of 10 male and 10 female Sprague-Dawley rats given 90, 440, or 1,750 mg/kg/day MTBE by gavage, 5 days/week had increased relative liver weight at 1,750 mg/kg/day (ITT Research Institute 1992).

Agency Contact (Chemical Manager): Moiz Mumtaz
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.
APPENDIX B

(2) **Exposure Period**  Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) **Health Effect**  The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the “System” column of the LSE table (see key number 18).

(4) **Key to Figure**  Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 “18r” data points in Figure 2-1).

(5) **Species**  The test species, whether animal or human, are identified in this column. Section 2.5, “Relevance to Public Health,” covers the relevance of animal data to human toxicity and Section 2.3, “Toxicokinetics,” contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) **Exposure Frequency/Duration**  The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number IS), 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.

(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 to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).

(17) **CEL** Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) **Estimated Upper-Bound Human Cancer Risk Levels** This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (ql*).

(19) **Key to LSE Figure** The Key explains the abbreviations and symbols used in the figure.
<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>
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<td>18</td>
<td>Rat</td>
<td>13 wk</td>
<td>Resp</td>
<td>3</td>
<td>10 (hyperplasia)</td>
<td>Nitschke et al. 1981</td>
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CHRONIC EXPOSURE

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<td>Rat</td>
<td>89–104 wk</td>
<td>15</td>
<td>5d/wk</td>
<td>6hr/d</td>
<td></td>
<td>NTP 1982</td>
</tr>
<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk</td>
<td>15</td>
<td>5d/wk</td>
<td>6hr/d</td>
<td></td>
<td>NTP 1982</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> 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)
  - Systemic
    - Death
    - Respiratory
    - Hematological

**Intermediate**

- (15-364 days)
  - Systemic
    - 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)
- □ 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 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Banes 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

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 and Prevention
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
F₀  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
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
Kₐ  adsorption ratio
kg  kilogram
kg  metric ton
K₀c  organic carbon partition coefficient
Kₐw  octanol-water partition coefficient
L  liter
LC  liquid chromatography
LC_{10}  lethal concentration, low
LC_{50}  lethal concentration, 50% kill
LD_{10}  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
mmHg  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
RFID  Reference Dose
RTCECS  Registry of Toxic Effects of Chemical Substances
sec  second
SCE  sister chromatid exchange
SIC  Standard Industrial Classification
SMR  standard mortality ratio
STEL  short term exposure limit
STORET  STORAGE and RETRIEVAL
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>TLV</td>
<td>threshold limit value</td>
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<tr>
<td>TSCA</td>
<td>Toxic Substances Control Act</td>
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<tr>
<td>TRI</td>
<td>Toxics Release Inventory</td>
</tr>
<tr>
<td>TWA</td>
<td>time-weighted average</td>
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<td>United States</td>
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<tr>
<td>UF</td>
<td>uncertainty factor</td>
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<td>yr</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>&gt;</td>
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<td>greater than or equal to</td>
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