APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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 agency wide 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.
TOLUENE

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET(S)

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 17
Species: human

MRL: [ ] mg/kg/day [X] ppm [ ] mg/m³


Experimental design: The effects of toluene on 16 healthy young male subjects with no previous regular exposure to organic solvents were investigated. Groups of four subjects were in a chamber for 6 hours a day on 4 consecutive days. After 1 hour of exposure to clean air in the chamber, the concentration of toluene was steadily increased during 30 minutes to the concentration intended for the day. After 1 hour of exposure, all subjects went through all physiological, discomfort, and performance measurements for the next 1.5 hours. After a 1 hour lunch, a similar series of measurements were made during the 5th and 6th hours of exposure. The concentration of toluene was 0, 10, 40, or 100 ppm with each group exposed to a different toluene concentration each day. Physiological measurements were performed, including nasal mucociliary flow, FVC, FEV, and FEF25-75, and subjective measurements of discomfort. Eight different performance assessment tests (five-choice serial reaction test, rotary pursuit test, screw-plate test, Landolt’s ring test, Bourdon Wiersma test, multiplication test, sentence comprehension test, and word memory test) were carried out.

Effects noted in study and corresponding doses: There was a significant change in nasal mucus flow from control values during all of the toluene exposures. During the 100 ppm exposure, statistically significant increased irritation was experienced in the eyes and in the nose, but not in the throat or lower airways. There was also a statistically significant increase in the occurrence of headaches, dizziness, and feelings of intoxication during the 100 ppm exposure, but not during the other concentrations. No statistically significant effects of toluene occurred in the eight performance tests. For three of the tests, multiplication test, Landolt’s rings, and the screw plate test, there was a borderline correlation between toluene and the test results. The subjects felt that the tests were more difficult and strenuous during the 100 ppm exposure, for which headache, dizziness, and feelings of intoxication were more often reported. No adverse effects were reported at the 10 and 40 ppm levels.

Dose endpoint used for MRL derivation: 40 ppm for neurological effects

[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)

MRL = 40 ppm x 5 days/7 days x 8 hours/24 hours ÷10 = 1 ppm (3.8 mg/m³)

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: Not applicable

Was a conversion used from intermittent to continuous exposure? Exposure concentration was adjusted to continuous exposure basis as shown above.

Other additional studies or pertinent information that lend support to this MRL: The primary effect of toluene is on the central nervous system. There are several other human studies for which the central nervous system is the major end point and could have been used to derive an acute inhalation MRL. However, the Andersen et al. (1983) study was chosen as the basis for the MRL because this was the only human study which reported a NOAEL. Baelum et al. (1985) also reported a LOAEL of 100 ppm for neurological effects in humans. In this study, 43 occupationally-exposed subjects and 43 controls were exposed to either clean air or air containing 100 ppm toluene for 6.5 hours in a climate chamber. A battery of ten tests of visuomotor coordination, visual performance, and cortical function were administered during the 6.5 hour period. For both the controls and toluene exposed subjects, there were complaints of air quality, irritation of the nasal passages, and increased feelings of fatigue and sleepiness. Subjects also complained of headaches and dizziness. Toluene exposure decreased performance on four of the neurobehavioral tests; three of these were tests of visual perseverance. The fourth test affected was the simple peg board test of visuomotor function, where the effect was noted in toluene-exposed workers to a much greater extent than controls. Escheverria et al. (1991) reported a LOAEL of 75 ppm for neurological effects in humans. In this study, two groups of 42 students were exposed to 0, 75, and 150 ppm toluene for a 7 hour period. A complete battery of 12 tests was administered before and at the end of each exposure. Toluene caused a dose-related impairment of function on digit span pattern recognition, the one hole test, and pattern memory. Rahill et al. (1996) reported a LOAEL of 100 ppm for neurological effects in humans. In this study, six volunteers were exposed for 6 hours a day to either 100 ppm toluene or clean air. Three repetitions of two computerized neuropsychological tests were performed, with the composite score on the multitasking test being significantly lower with toluene exposure than with clean air.

Agency Contact (Chemical Manager): Alfred Dorsey
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 160
Species: human

MRL: 0.08 [ ] mg/kg/day [X] ppm [ ] mg/m³


Experimental design: Three groups of Croatian workers were examined by means of interviews, medical examination, and color vision testing using the Lanthony 15 Hue desaturated panel in standard conditions. Workers were excluded from the study if they met any of the following criteria: less than 6 months employment, congenital color vision loss, a medical condition which can affect color vision, visual acuity below 6/10, use of medications which can affect color vision or a hobby that involved solvent exposure. Alcohol intake and smoking were also assessed for each individual. The first group consisted of 46 workers (43 women and 3 men) employed in manually gluing shoe soles and exposed to median levels of 32 ppm and geometric mean levels of 35 ppm toluene. The second group consisted of 37 workers (34 men and 3 women) employed in a rotogravure printing press and exposed to median levels of 132 ppm and geometric mean levels of 156 ppm toluene. The third group consisted of 90 workers (61 men and 29 women) not occupationally exposed to any solvents or known neurotoxic agents. The average age of the workers was 41 years. The technology, ventilation and types of workplaces included in the study had not changed in the preceding 30 years. Toluene exposure was evaluated by mid-week environmental and biological monitoring of toluene. Samples of air were collected at 11 stations in the shoe factory and 8 locations in the printing press. Toluene levels were measured in blood samples taken at the beginning of the work shift (all workers). Orthocresol and hippuric acid levels in urine were measured (for printers only) at the end of the work shift.

Effects noted in study and corresponding doses: Comparison of mean values between groups was assessed by t-test or Mann-Whitney U-test. Correlations between variables were determined using linear multiple regression analyses. Analyses were performed using CCI or AACC1 as dependent factors and age, alcohol intake, exposure duration, work service, toluene in air, toluene in blood, and biological markers of toluene in urine (printers only) as independent factors. A p-value <0.05 was regarded as significant. The mean CCI was significantly higher in printers compared to both shoemakers and controls. The Mean CCI for shoemakers was increased compared with controls, but the difference was not significant. Regression analysis of the control data indicated that alcohol intake and age were significant explanatory variables for changes in CCI. The age- and alcohol-adjusted color confusion index was significantly increased in printers (156 ppm) compared with both shoemakers (35 ppm) and controls, and in shoemakers (35 ppm) compared with controls. Regression analyses of the data from printers showed significant correlations between CCI as a dependent variable and age, alcohol intake, toluene in air, toluene in blood, hippuric acid in urine, or orthocresol in urine as independent variables.
Significant correlation was also found for AACCI as dependent variable and exposure to toluene or biomarkers of toluene exposure. In contrast, the shoemaker data showed a significant correlation between CCI and age, but did not establish any significant correlation between CCI or AACCI and any marker of toluene exposure. This study demonstrated a statistically significant impairment of color vision in workers chronically exposed to 156 ppm toluene compared with controls. When the data were adjusted to allow for the confounding effects of alcohol consumption and age, a significant difference due to toluene exposure was also reported for workers exposed to 35 ppm toluene compared with controls.

Dose endpoint used for MRL derivation: 35 ppm for alcohol-and age-adjusted color vision impairment

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

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

MRL = 35 ppm x 5 days/7 days x 8 hours/24 hours ÷ 100 = 0.08 ppm (0.3 mg/m³)

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: Not applicable.

Was a conversion used from intermittent to continuous exposure? Exposure concentration was adjusted to continuous exposure basis as shown above.

Other additional studies or pertinent information that lend support to this MRL: There are several other reports of subtle neurological impairments in toluene-exposed workers that support this MRL. Another group of printers exposed to mean concentrations of 120 ppm toluene had a significantly increased mean alcohol-and age-adjusted color confusion index compared with unexposed controls (Zavalic et al. 1998b). A group of printing press workers (exposed to average toluene concentrations of 50 ppm for an average of 30 years) had significantly reduced wave amplitude of visual evoked potentials and increased latency of auditory evoked potentials (Vrca et al. 1995, 1996, 1997a, 1997b). Significant changes in auditory evoked potentials were also reported for printers exposed to 97 ppm toluene for 12–14 years (Abbate et al. 1993). A study of hearing loss in Brazilian printers exposed to multiple solvents (toluene concentrations in air were reported as 0.14–919 mg/m³ or 0.04–245 ppm) found that the odds ratio for hearing loss increased 1.76 times with each gram of hippuric acid/gram creatinine (Morata et al. 1997). Ten rotogravure printers (average exposure of 83 ppm for 1–36 years) examined for neurological effects were found to have a lower coefficient of variation in electrocardiographic R-R intervals than 10 age-matched controls (Murata et al. 1993). Significant deficits in 28 of 30 neurobehavioral tests were found for a group of electronics workers exposed to TWA concentrations of 88 ppm toluene for an average of 6 years compared with unexposed controls (Foo et al. 1990). Boey et al. (1997) also found significant deficits in neurological tests for electronics workers (exposed to TWA concentrations of 90.9 ppm toluene) compared with unexposed controls. Orbaek and Nise (1989) reported increased neurasthenic symptoms and performance deficits in psychometric tests for printers from two plants exposed to toluene for 4–43 years (median 29 years). At the time of the study (1985), TWA levels in the two plants were 11.4 and 41.7 ppm, but previous concentrations were higher, with estimated midpoints for each plant of 132 and 147 ppm and the mean of these midpoints, 140 ppm, can be taken as a representative exposure
concentration for the overall group. In general, these studies corroboratively demonstrate that subtle neurological effects can occur from repeated exposure to toluene concentrations within the range of 32–150 ppm.

Agency Contact (Chemical Manager): Alfred Dorsey
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 10
Species: rat

MRL: 0.8 [X] mg/kg/day [ ] ppm [ ] mg/m³


Experimental design: Male Long-Evans rats (12 per group) were administered doses of toluene in corn oil of 0, 250, 500, and 1,000 mg/kg/day by gavage. Flash-evoked potential tests were administered 45 minutes later as a test of the ability of the nervous system to process visual information. In another study (time-course), toluene was administered to male Long-Evans rats (16 per group) at doses of 0 and 500 mg/kg/day by gavage and flash-evoked potential tests were performed 4, 8, 16, and 30 hours later.

Effects noted in study and corresponding doses: The amplitude of the N3 peak of the flash-evoked potential was significantly decreased (P<0.05) by toluene exposure at all doses. This decrease in peak amplitude was not dose-related. In the time course study, 500 mg/kg/day also decreased the amplitude of the flash-evoked potential; at this dose, little change in magnitude of peak N3 depression had occurred 8 hours post treatment; by 16 hours recovery was complete.

Dose endpoint used for MRL derivation: 250 mg/kg/day for neurological effects

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 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)

MRL = 250 mg/kg/day ÷ 300 = 0.8 mg/kg/day

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: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.
Other additional studies or pertinent information that lend support to this MRL: Although no additional acute oral animal studies are available on the neurological effects of toluene, a number of animal inhalation studies have reported neurological effects from toluene (Arito et al. 1988; Bushnell et al. 1994; Carpenter et al. 1986; Harabuchi et al. 1993; Hinman 1987). Human inhalation studies have shown the central nervous system to be the major end point for toluene exposure (Andersen et al. 1983; Baelum et al. 1985; Escheverria et al. 1991; Rahill et al. 1996).

Agency Contact (Chemical Manager): Alfred Dorsey
MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Toluene
CAS number: 108-88-3
Date: June 8, 2000
Profile status: Post-public Draft 3/Camera Ready
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 29
Species: mouse

MRL: 0.02 [X] mg/kg/day [ ] ppm [ ] mg/m³


Experimental design: Male CD-1 mice (5 per group) were administered toluene in their drinking water for a 28-day period. Based on water consumption and average toluene concentrations, the authors calculated toluene doses for the four treatment doses of 0, 5, 22, and 105 mg/kg/day over this period. Brain levels of norepinephrine, dopamine, serotonin, 3-methoxy-4-hydroxymandelic acid, 3,4-dihydroxyphenylacetic acid, homovanillic acid, and 5-hydroxyindolacetic acid were measured in six areas of the brain in the mice. A level of P<0.05 was considered statistically significant unless otherwise stated.

Effects noted in study and corresponding doses: Significant increases in norepinephrin were present in the hypothalamus and in the midbrain in groups treated with 5, 22, and 105 mg/kg/day toluene. Toluene also increased serotonin levels, with the increase being maximal at 22 mg/kg/day in the midbrain (P<0.005) and cerebral cortex (P<0.005). A significant increase was also seen in the hypothalamus with norepinephrine, dopamine, and serotonin (P<0.005). In the corpus striatum, the levels of dopamine and serotonin were significantly increased at the two highest doses. In the medulla oblongata, significant toluene increases of norepinephrine and homovanillic acid were seen only at 22 mg/kg/day.

Dose endpoint used for MRL derivation: 5 mg/kg/day for neurological effects

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 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)

MRL = 5 mg/kg/day ÷ 300 = 0.02 mg/kg/day

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: Not applicable.
**Was a conversion used from intermittent to continuous exposure?** No.

**Other additional studies or pertinent information that lend support to this MRL:** The effects reported in the Hsieh et al. (1990b) study are minimal effects, and it is unclear how they are related to neurobehavioral changes. These results support the possible involvement of monoamine metabolism in the reported behavioral and neurophysiological effects of toluene. Alterations in the brain concentrations of neurotransmitters and their metabolites have been correlated with abnormal behavioral and physiological functions.

Although no additional intermediate oral animal studies are available on the neurological effects of toluene, a number of animal inhalation studies have reported neurological effects from toluene (Arito et al. 1988; Bushnell et al. 1994; Carpenter et al. 1986; Harabuchi et al. 1993; Hinman 1987). Human inhalation studies have shown the central nervous system to be the major endpoint for toluene exposure (Andersen et al. 1983; Baelum et al. 1985; Escheverria et al. 1991; Rahill et al. 1996).

An additional study that lends support to the MRL is a developmental study in which impaired rotorod performance and motor coordination were reported in the offspring of mice exposed to 4, 21, and 106 mg/kg/day (Kostas and Hotchin 1981). Pregnant mice were exposed to toluene in their drinking water throughout pregnancy and lactation. From weaning at 21 days of age until postnatal day 55, the pups were exposed to toluene in their drinking water. The dose levels received by the pups cannot be accurately determined because the exposure occurred in utero, during lactation, and also via drinking water. The neurobehavioral effects reported in the offspring support the MRL; however, the impairment of rotorod performance was not dose-related.

**Agency Contact (Chemical Manager):** Alfred Dorsey
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 2-1).

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

(6) **Exposure Frequency/Duration**  The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) **System**  This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) **NOAEL**  A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) **LOAEL**  A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific 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 (q₁*).

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

<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Species</th>
<th>Exposure frequency/duration</th>
<th>System</th>
<th>NOAEL (ppm)</th>
<th>LOAEL (effect)</th>
<th>Less serious (ppm)</th>
<th>Serious (ppm)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INTERMEDIATE EXPOSURE**

- **Systemic** 9
  - 13 wk
  - 5d/wk
  - 6hr/d

**CHRONIC EXPOSURE**

- **Cancer**
  - 18 mo
  - 5d/wk
  - 7hr/d

- **Rat**
  - 89–104 wk
  - 5d/wk
  - 6hr/d

- **Mouse**
  - 79–103 wk
  - 5d/wk
  - 6hr/d

---

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

b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5 \times 10^{-7}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)
Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation

**Acute**
(≤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
- ▼ The number next to each point corresponds to entries in the accompanying table.

* 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 2.8, "Interactions with Other Substances," and 2.9, "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>ADI</td>
<td>Acceptable Daily Intake</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism, and Excretion</td>
</tr>
<tr>
<td>AFID</td>
<td>alkali flame ionization detector</td>
</tr>
<tr>
<td>AFOSH</td>
<td>Air Force Office of Safety and Health</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>AOAC</td>
<td>Association of Official Analytical Chemists</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>AWQC</td>
<td>Ambient Water Quality Criteria</td>
</tr>
<tr>
<td>BAT</td>
<td>Best Available Technology</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>CAA</td>
<td>Clean Air Act</td>
</tr>
<tr>
<td>CAG</td>
<td>Cancer Assessment Group of the U.S. Environmental Protection Agency</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Services</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CEL</td>
<td>Cancer Effect Level</td>
</tr>
<tr>
<td>CELDS</td>
<td>Computer-Environmental Legislative Data System</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>CL</td>
<td>ceiling limit value</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>CPSC</td>
<td>Consumer Products Safety Commission</td>
</tr>
<tr>
<td>CWA</td>
<td>Clean Water Act</td>
</tr>
<tr>
<td>d</td>
<td>day</td>
</tr>
<tr>
<td>Derm</td>
<td>dermal</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>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>DOE</td>
<td>Department of Energy</td>
</tr>
<tr>
<td>DOL</td>
<td>Department of Labor</td>
</tr>
<tr>
<td>DOT</td>
<td>Department of Transportation</td>
</tr>
<tr>
<td>DOT/UN/</td>
<td>Department of Transportation/United Nations/</td>
</tr>
<tr>
<td>NA/IMCO</td>
<td>North America/International Maritime Dangerous Goods Code</td>
</tr>
<tr>
<td>DWEL</td>
<td>Drinking Water Exposure Level</td>
</tr>
<tr>
<td>ECD</td>
<td>electron capture detection</td>
</tr>
<tr>
<td>ECG/EKG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>EEGL</td>
<td>Emergency Exposure Guidance Level</td>
</tr>
<tr>
<td>EPA</td>
<td>Environmental Protection Agency</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>FDA</td>
<td>Food and Drug Administration</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>FPD</td>
<td>flame photometric detection</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>Federal Register</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>Gd</td>
<td>gestational day</td>
</tr>
<tr>
<td>gen</td>
<td>generation</td>
</tr>
<tr>
<td>GLC</td>
<td>gas liquid chromatography</td>
</tr>
<tr>
<td>GPC</td>
<td>gel permeation chromatography</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>hr</td>
<td>hour</td>
</tr>
<tr>
<td>HRGC</td>
<td>high resolution gas chromatography</td>
</tr>
<tr>
<td>HSDB</td>
<td>Hazardous Substance Data Bank</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>IRIS</td>
<td>Integrated Risk Information System</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>
</tr>
<tr>
<td>L</td>
<td>liter</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>LC&lt;sub&gt;Lo&lt;/sub&gt;</td>
<td>lethal concentration, low</td>
</tr>
<tr>
<td>LC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>lethal concentration, 50% kill</td>
</tr>
<tr>
<td>LD&lt;sub&gt;Lo&lt;/sub&gt;</td>
<td>lethal dose, low</td>
</tr>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt;</td>
<td>lethal dose, 50% kill</td>
</tr>
<tr>
<td>LT&lt;sub&gt;50&lt;/sub&gt;</td>
<td>lethal time, 50% kill</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect level</td>
</tr>
<tr>
<td>LSE</td>
<td>Levels of Significant Exposure</td>
</tr>
<tr>
<td>m</td>
<td>meter</td>
</tr>
<tr>
<td>MA</td>
<td>trans, trans-muconic acid</td>
</tr>
<tr>
<td>MAL</td>
<td>Maximum Allowable Level</td>
</tr>
<tr>
<td>mCi</td>
<td>millicurie</td>
</tr>
<tr>
<td>MCL</td>
<td>Maximum Contaminant Level</td>
</tr>
<tr>
<td>MCLG</td>
<td>Maximum Contaminant Level Goal</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
</tbody>
</table>
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
NAAQS National Ambient Air Quality Standard
NAS National Academy of Science
NATICH National Air Toxics Information Clearinghouse
NATO North Atlantic Treaty Organization
NCE normochromic erythrocytes
NCI National Cancer Institute
NIEHS National Institute of Environmental Health Sciences
NIOSH National Institute for Occupational Safety and Health
NIOSHTIC NIOSH's Computerized Information Retrieval System
NFPA National Fire Protection Association
ng nanogram
NLM National Library of Medicine
nm nanometer
NHDRES National Health and Nutrition Examination Survey
nmol nanomole
NOAEL no-observed-adverse-effect level
NOES National Occupational Exposure Survey
NOHS National Occupational Hazard Survey
NPD nitrogen phosphorus detection
NPDES National Pollutant Discharge Elimination System
NPL National Priorities List
NR not reported
NRC National Research Council
NS not specified
NSPS New Source Performance Standards
NTIS National Technical Information Service
NTP National Toxicology Program
ODW Office of Drinking Water, EPA
OERR Office of Emergency and Remedial Response, EPA
OHM/TADS Oil and Hazardous Materials/Technical Assistance Data System
OPP Office of Pesticide Programs, EPA
OPPTS Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT Office of Pollution Prevention and Toxics, EPA
OSHA Occupational Safety and Health Administration
OSW Office of Solid Waste, EPA
OTS Office of Toxic Substances
OW Office of Water
OWRS Office of Water Regulations and Standards, EPA
PAH Polycyclic Aromatic Hydrocarbon
PBPD Physiologically Based Pharmacodynamic
PBPK Physiologically Based Pharmacokinetic
PCE polychromatatic erythrocytes
PEL permissible exposure limit
PID photo ionization detector
pg  picogram
pmol  picomole
PHS  Public Health Service
PMR  proportionate mortality ratio
ppb  parts per billion
ppm  parts per million
ppt  parts per trillion
PSNS  Pretreatment Standards for New Sources
REL  recommended exposure level/limit
RfC  Reference Concentration
RfD  Reference Dose
RNA  ribonucleic acid
RTECS  Registry of Toxic Effects of Chemical Substances
RQ  Reportable Quantity
SARA  Superfund Amendments and Reauthorization Act
SCE  sister chromatid exchange
sec  second
SIC  Standard Industrial Classification
SIM  selected ion monitoring
SMCL  Secondary Maximum Contaminant Level
SMR  standard mortality ratio
SNARL  Suggested No Adverse Response Level
SPEGL  Short-Term Public Emergency Guidance Level
STEL  short-term exposure limit
STORET  Storage and Retrieval
TD$_{50}$  toxic dose, 50% specific toxic effect
TLV  threshold limit value
TOC  Total Organic Compound
TPQ  Threshold Planning Quantity
TRI  Toxics Release Inventory
TSCA  Toxic Substances Control Act
TRI  Toxics Release Inventory
TWA  time-weighted average
U.S.  United States
UF  uncertainty factor
VOC  Volatile Organic Compound
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
α  alpha
β  beta
γ  gamma
δ  delta
μm  micrometer
µg  microgram
q₁  cancer slope factor
–  negative
+  positive
(+) weakly positive result
(−) weakly negative result