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.

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: 1 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Andersen I, Lundqvist GR, Molhave L et al. 1983. Human response to controlled levels of toluene in six-hour exposures. Scand J Work Environ Health 9: 405-418.

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 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 FEF_{25-75}, 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/m^3)

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/m^3

References: Zavalic, M, Mandic, Z, Turk, R et al. 1998a. Quantitative assessment of color vision impairment in workers exposed to toluene. Am J Ind Med 32: 297-304.

Zavalic, M, Mandic, Z, Turk, R et al. 1988c. Assessment of colour vision impairment in male workeres exposed to toluene generally above occupational exposure limits. Occup Med 48(3):175-180

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 glueing 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 AACCI 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/m^3)

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 expsoure 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/m^3 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/m^3

Reference: Dyer RS, Bercegeay MS, Mayo LM. 1988. Acute exposures to *p*-xylene and toluene alter visual information processing. Neurotoxicol Teratol 10: 147–153.

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/m^3

Reference: Hsieh GC, Sharma RP, Parker RDR et al. 1990b. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotox Environ Safety 20: 175–184.

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 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/m^3 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 (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6 **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 6	Systemic	9	9	9	9	9		9
4 6	18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
							11	
	Cancer						9	
	38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

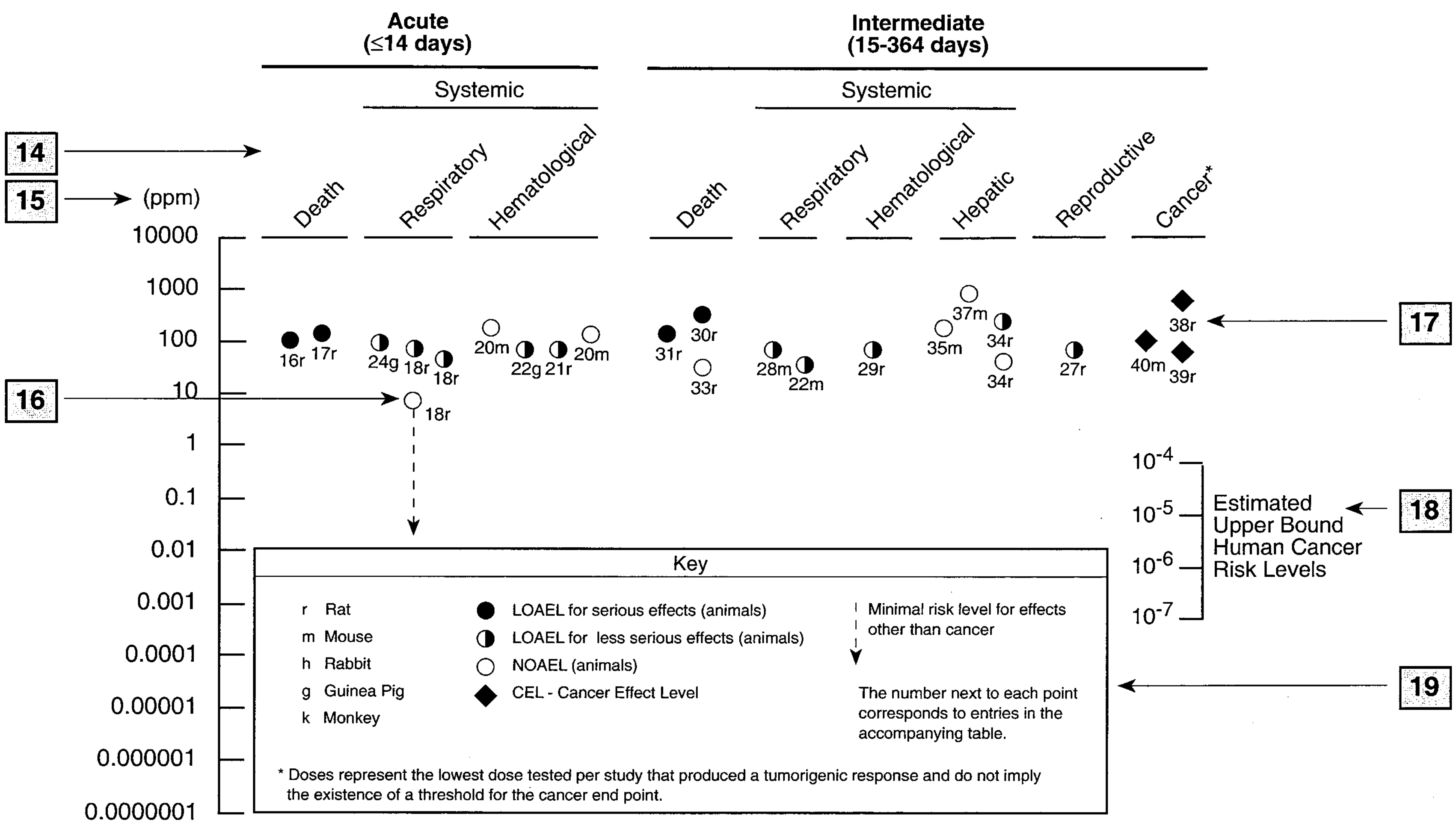
[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} 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)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



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

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
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
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic 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
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
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	polychromatic 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
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer

μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result