APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, 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 (l-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.

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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 hundred fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL

Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: October 1996
Profile Status: Post-Public Comments
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 16
Species: Human

Minimal Risk Level: 0.2 [ ] mg/kg/day [x] ppm

Reference: Altmann et al. 1992

Experimental design:

Male volunteers were exposed to tetrachloroethylene at 10 or 50 ppm for 4 hours/day for 4 days. A total of 28 subjects were exposed; 12 at 10 ppm, 16 at 50 ppm. The 10 ppm concentration was considered the control exposure and was used because it exceeded the odor threshold of tetrachloroethylene. Therefore, the subjects were supposedly blinded to the exposure conditions. Altmann et al. (1992) state that faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing leading the investigators to conclude that only a few subjects could identify their exposure condition.

Pattern reversal and pattern onset visual-evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and tests of cognitive and psychomotor performance, and mood ratings were completed 72 hours before exposure, and during or after the exposure. VEPs and BAEPs were measured after 2 hours of exposure. Peak latencies of three components of VEPs (N75, Pl00 and N150) were measured. Measurements were made at the same time each day (10 AM-12 PM) to exclude circadian variations. The test battery completed included finger tapping, eye-hand coordination using a sine wave tracking test, simple reaction times, a continuous performance test, symbol-digit test, visual retention, pattern recognition test, digit learning, paired associates learning and retention, vocabulary test, and mood scales. Blood concentrations of tetrachloroethylene were measured before each day's exposure, in the middle of the exposure and at the end of the exposure.

Effects noted in study and corresponding doses:

At 50 ppm, pattern reversal VEP latencies increased over the course of the exposure period, while at 10 ppm, pattern reversal VEP latencies decreased as a result of training. The difference-between the two groups was statistically significant ($p<0.05$). No effect on pattern onset VEPs or BAEPs were noted.

Using analysis of covariance, with preexposure baseline values as the covariates, significant performance deficits for vigilance ($p=0.04$), and eye-hand coordination ($p=0.05$) as well as a borderline increase in simple reaction times ($p=0.09$) at 50 ppm were found. For these tests, both exposure groups improved over the course of the experiment, but there was a greater improvement in the

10 ppm group compared to the 50 ppm group. No significant effects were noted for the tapping tests, or the learning and memory tests, or mood ratings.

Tetrachloroethylene in the blood increased with exposure duration. By the end of the last exposure period, tetrachloroethylene concentrations "exceeded 1.5 mg/L, and 0.3 mg/L" at 50 and 10 ppm, respectively.

Dose and endpoint used for MRL derivation:

[x] NOAEL [ ] LOAEL

10 ppm

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

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

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

To extrapolate from intermittent exposure, the 10 ppm concentration was multiplied by 4/24 hours.

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

In a similar study by Altmann et al. (1990), increased latencies ($p<0.05$) for pattern reversal VEPs were observed in 10 male volunteers exposed to tetrachloroethylene at 50 ppm, compared to 12 men exposed at 10 ppm. Exposures in this study were also 4 hours/day for 4 days. Effects on BAEPs were also not observed in the Altmann et al. (1990) study. Tetrachloroethylene in the blood increased with exposure duration, and linear regression to associate blood tetrachloroethylene with pattern reversal VEP latencies was significant ($r = -0.45$, $p<0.03$). Additional tests of neurological function were not completed in this study.

Hake and Stewart (1977) did not find any changes in flash evoked potentials (FEPs) and equilibrium tests in 4 male subjects exposed to increasing concentrations of tetrachloroethylene for 7.5 hours/day for 5 days. The subjects were sequentially exposed to 0, 20, 100 and 150 ppm (each concentration 1 week). Subjective evaluation of EEG scores suggested cortical depression in subjects-exposed at 100 ppm. Decreases in the Flanagan coordination test were observed at ≥100 ppm. No significant changes in FEPs were observed. Otto et al. (1988) notes that FEPs are subject to large inter- and intrasubject variability of waveforms, and that pattern reversal VEPs are more useful clinically than FEPs. Therefore, the lack of effect on FEPs at 100 ppm in the Hake and Stewart (1977) study may reflect the lower sensitivity of the FEPs compared to the pattern reversal VEPs. The Hake and Stewart (1977) study does confirm that the nervous system is a sensitive target in humans. Rao et al. (1993) completed a logistic regression analysis of tetrachloroethylene toxicity data and concluded that the nervous system was a sensitive target of tetrachloroethylene toxicity in humans.

Acute studies in animals have reported serious effects at much higher concentrations. Hypoactivity and ataxia were observed in rats following a 2 week exposure (6 hours/day, 5 days/week) at 1750 ppm (NTP 1986). Anesthesia has been reported in mice exposed to tetrachloroethylene at 2328 ppm for 4 hours and 1750 ppm for 2 weeks (6 hours/day, 5 days/week) (NTP 1986). The lowest LOAEL in an acute study in animals was 200 ppm for fatty degeneration of the livers of mice exposed to tetrachloroethylene for 4 hours (Kylin et al. 1963). Therefore, the comparison of animal and human data following acute inhalation exposure suggests that humans are more sensitive to tetrachloroethylene, or that sensitive neurological endpoints have not been examined in animal studies.

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Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: October 1996
Profile Status: Post-Public Comments
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 64
Species: Human

Minimal Risk Level: 0.04 [ ] mg/kg/day [x] ppm

Reference: Ferroni et al. 1992

Experimental design:

Neurobehavioral effects were studied in 60 women exposed to tetrachloroethylene in dry cleaning shops for an average of 10.1 years. Thirty women who worked at a cleaning plant where solvents were not used served as controls. Tetrachloroethylene levels were measured in blood samples collected during the work day and in air samples collected over 4-hour periods during the workweek. Blood and air samples were taken during the summer and winter to allow for seasonal variation. The median tetrachloroethylene concentration in air was 15 ppm (range l-67 ppm), and the median tetrachloroethylene blood concentration was 145 mg/L (range 12-864 mg/L). Neurobehavioral tests completed were: finger tapping with dominant and nondominant hands, simple reaction times, digit symbol, shape comparison in two versions to test vigilance and the response to stress. It is not clear when in relation to the working day the neurobehavioral tests were completed.

Effects noted in study and corresponding doses:

Tetrachloroethylene-exposed workers had increased reaction times in all tests: simple reaction times, exposed 259 ± 40, controls 235 ±22, $p<0.0001$; shape comparison - vigilance, exposed 635 ± 68, controls 589 ± 72, $p<0.005$; shape comparison - stress, exposed 557 ± 66, controls 501 ±72, $p<0.005$. The duration of exposure and tetrachloroethylene blood levels were not significantly correlated with performance test scores.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

15 ppm, increased reaction times

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 10 for human variability

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

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

To convert from occupational exposure to continuous exposure, the 15-ppm concentration was multiplied by 8/24 hours and 5/7 days.

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

The nervous system is a well established target of tetrachloroethylene exposure in humans, and logistic regression of toxicity data suggests that it may be the most sensitive target (Rao et al. 1993). Cai et al. (1991) reported increased subjective symptoms including dizziness and forgetfulness in workers exposed to tetrachloroethylene at an average of 20 ppm for l-120 months. Exposure was measured using diffusive sampling with carbon cloth. Additional details were not provided. In a study in which the duration of exposure is unclear (Seeber 1989), perceptual speed and digit reproduction as a memory test were impaired in workers exposed to an average of 12 ppm. No detrimental effects on critical flicker fusion, simple and g-choice visual reaction time and a sustained attention test were observed in 22 workers exposed to tetrachloroethylene at an average of 21 ppm for about 6 years (Lauwerys et al. 1983). In this study, the neurological function tests were completed both before and after work so that training effects and effects of tetrachloroethylene exposure on learning may have contributed to the difference between the Ferroni et al. (1992) study and the Lauwerys et al. (1983). Although exposure measurements were more comprehensive in the Lauwerys et al. (1983) study (the investigators measured urine trichloroacetic acid daily for one week, air concentrations with personal air samplers and badges and breath and blood concentrations of tetrachloroethylene), the measurements were completed during one week, while in the Ferroni et al. (1992) study, the more limited measurements were completed during the summer and winter and may better represent chronic exposure.

Loss of color vision has also been reported in dry cleaners exposed to tetrachloroethylene at an average of 7.3 ppm for an average of 106 months (Cavalleri et al. 1994). Although this study seems to identify an effect at a lower concentration than the Ferroni et al. (1992) study, fewer subjects were studied (n=22 exposed subjects), and exposure concentrations were only measured in air on one day, while Ferroni et al. (1992) completed air and blood measurements in both the winter and summer. In addition, no effect on blue-yellow color vision was noted in 30 men, or in 34 women occupationally exposed to tetrachloroethylene at average concentrations of 15.3 and 10.7 ppm, respectively (Nakatsuka et al. 1992). Therefore, because of inconsistent reports on the effect of tetrachloroethylene on color vision, and because of the better exposure assessment and the larger number of subjects (n=60) in the Ferroni et al (1992) study compared to the Cavallari et al. (1994) study, the Ferroni et al. (1992) study was chosen as the basis for the MRL.

An additional study did not report any effects on neurological function among 14 persons who lived above or next to dry cleaning facilities for 1 to 30 years compared to 23 controls matche-d for age (±l year, in two cases 3 and 5 years) and gender when the absolute values of the tests were examined (Altmann et al. 1995). Median tetrachloroethylene exposure concentrations were 0.2 ppm in the apartments of the exposed individuals, and 0.0003 ppm in the apartments of control subjects, and blood concentrations were 17.8 ±46.9 μg/L in exposed, and less than the detection limit of 0.5 μg/L in the control individuals. When multivariate analysis was completed to adjust for age, gender, and education, an increased response time in a continuous performance test, increased simple reaction time to a visual stimuli, and decreased performance in a test of visual memory were observed. No effect on pattern reversal visual-evoked potentials was observed. The 0.2 ppm concentration is considered a

NOAEL because of the lack of effect on the absolute values of the tests. This study does suggest that further studies of larger populations exposed to very low levels of tetrachloroethylene would be useful.

Additional studies of workers exposed to relatively low concentrations of tetrachloroethylene have also reported minor indicators of renal tubular damage. Franchini et al. (1983) reported increased urinary levels of lysozyme and beta-glucuronidase in workers occupationally exposed to tetrachloroethylene at a time-weighted average of 10 ppm for an average of 14 years. Mutti et al. (1992) found increased urinary albumin, transferrin, the brush-border membrane antigens B50, BBA, and HF5, and tissue nonspecific alkaline phosphatase in workers exposed to an average tetrachloroethylene concentration of 15 ppm (measured in air over a wide period to account for seasonal variation) for an average of 10 years. Urinary fibronectin was significantly decreased relative to controls. The investigators concluded that the results showed increased shedding of epithelial membrane components from tubular cells. Vyskocil et al. (1990) found an increase in urinary lysozyme in workers exposed to tetrachloroethylene at an average of 23 ppm for 9 years. No effects on urinary β_2-microglobulin, creatinine, lysozyme activity, glucose, LDH, and total proteins were noted.

Other studies of renal function in workers occupationally exposed to tetrachloroethylene at relatively low TWA concentrations have not found any effects. Cai et al. (1991) found no effects on BUN or creatinine in workers exposed to an average of 20 ppm for l-120 months. Urinary β_2-microglobulin, retinol binding protein, and albumin were not affected in workers exposed to tetrachloroethylene at an average concentration of 21 ppm for 6 years (Lauwerys et al. 1983). Solet and Robins (1991) found no effects on total protein, albumin, *N*-acetyl-glucosaminidase, or creatinine in workers exposed to tetrachloroethylene at an average concentration of 14 ppm.

Although nervous system and mild kidney effects appear to occur at similar concentrations in persons occupationally exposed to tetrachloroethylene, the nervous system effects were considered a more appropriate basis for the MRL. The nervous system effects noted, decreased reaction times, could lead to serious accidents, and at higher concentrations, tetrachloroethylene clearly produces incoordination (Stewart et al. 1970). The significance of the mild kidney changes observed following low level occupational exposure to tetrachloroethylene is unknown. The kidney changes may be an adaptive effect rather than an adverse effect. In addition, in the study reporting kidney effects at 10 ppm (Franchini et al. 1983), the exposure level was estimated using urinary TCA concentrations, so the actual exposure concentrations are unknown.

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Chemical Name: Tetrachloroethylene
CAS Number: 127-18-4
Date: October 1996
Profile Status: Post-Public Comments
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 19
Species: Mouse

Minimal Risk Level: 0.05 [xl mg/kg/day [ ] ppm

Reference: Fredriksson et al. 1993

Experimental design:

Groups of 12 male NMRI mice from 3-4 different litters were treated by gavage with tetrachloroethylene in egg 1ecithin:peanut oil (10:l) at 0, 5, or 320 mg/kg/day for 7 days beginning at 10 days of age. The high dose was 5% of the $LD_{50}$and did not sedate the pups. Although the study indicates that female pups were dosed, results in female pups are not presented. At 17 and 60 days of age, behavioral testing (locomotion, rearing, total activity) was completed during three 20minute testing periods from 8 a.m.-12 p.m.

Effects noted in study and corresponding doses:

No symptoms of toxicity were observed throughout the experimental period, and there were no differences in body weight gain. No effects on behavior were noted when the animals were tested at 17 days of age. At 60 days of age, treated mice showed an increase in locomotion and total activity which was statistically different from controls ($p<0.05$ or $p<0.01$) at both doses and over the three 20-minute test periods. The increase in activity measures was similar at both doses. A significant decrease ($p<0.01$) in rearing was observed in mice treated only at the high dose during the first and second, but not the third, 20-minute test period. The investigators indicate that the results show a disruption of a simple nonassociative learning process, habituation. The mice were not followed to determine if the increase in activity persisted beyond 60 days.

The changes in behavior observed at the lowest dose (5 mg/kg/day) is a LOAEL and serves as the basis for the acute oral MRL.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

5 mg/kg/day, hyperactivity

Uncertainty Factors used in MRL derivation:

[x] 10 for use of a LOAEL
[xl 10 for extrapolation from animals to humans
[x] 1 for human variability

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

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

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

In a behavioral teratology study, pregnant Sprague-Dawley rats were exposed to 0, 100, or 900 ppm tetrachloroethylene on days 14-20 of gestation and to 0 or 900 ppm tetrachloroethylene on days 7-13 (Nelson et al. 1980). Effects occurred after exposure to 900 ppm for both exposure periods, but not after exposure to 100 ppm. Dams had reduced feed consumption and weight gain, without liver or kidney histological alterations. Pups of dams exposed to 900 ppm on gestation days 7-13 had decreased performance during tests of neuromuscular ability (ascent on a wire mesh screen and rotarod balancing) on certain days. Offspring (before weaning) from dams exposed to 900 ppm on days 14-20 performed poorly on the ascent test on test day 14 only, but later in development their performance in the rotarod balancing test was superior to the controls, and they were more active in an open-field test. Brains of 21-day-old offspring exposed to 900 ppm prenatally had significant decreases in neurotransmitters (dopamine in those exposed on gestation days 14-20 and acetylcholine in those exposed on days 7-13 or 14-20). The lower concentration (100 ppm) produced no significant differences from controls. There were no microscopic brain lesions.

This study confirms that behavioral effects can occur if exposure to tetrachloroethylene occurs while the nervous system is developing. Additional studies which determine if the effect is permanent, and studies in rats which may be a better model for neurological effects would increase the confidence in the use of developmental neurotoxicity as the end point for the development of the oral MRL.

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-l 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 upperbound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l 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-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

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

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

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

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

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

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

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(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 →

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
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

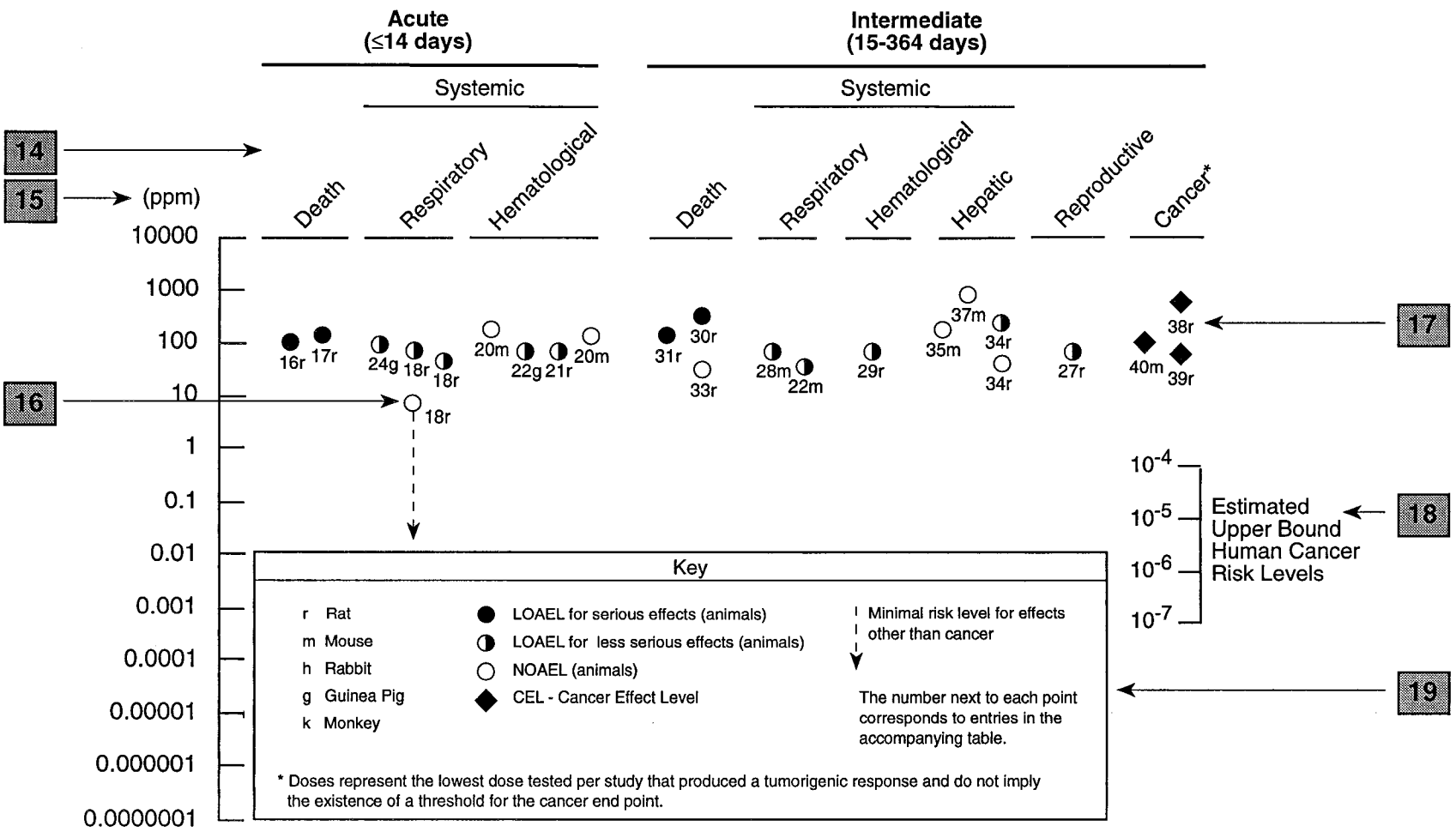
[a] The number corresponds to entries in Figure 2-1.

12 → [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 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX B

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-observedadverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
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
NCE	normochromatic erythrocytes
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million

ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram