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. 99-4991, 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 clea*n*-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.

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

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

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: *n*-Hexane
CAS number: 110-54-3
Date: May 19, 1999
Profile status: Draft 3, Post-public comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Key to figure: 69
Species: Human

MRL: 0.6   [ ] mg/kg/day [x] ppm [ ] mg/m³

Reference: Sanagi S, Seki Y, Sugimoto K, Hirata M. 1980. Peripheral nervous system functions of workers exposed to *n*-hexane at a low level. Int Arch Occup Environ Health. 47(1):69-79.

Experimental design: This is an epidemiology study on 2 age-matched groups consisting of 14 control workers and 14 exposed workers employed in a factory producing tungsten carbide alloys. The groups were matched with respect to age, stature, weight, alcohol consumption, and smoking habits. Exposure was estimated with 22 personal samples taken from the breathing zones over a period of 2 years (this number of samples is fewer than optimal for measuring air levels). The 8-hour time-weighted average exposure to solvent vapors consisted of *n*-hexane at 58±41 ppm and acetone at 39±30 ppm; no other solvent vapors were detected. The exposure duration ranged from 1 to 12 years, with an average of 6.2 years. Both groups completed questionnaires and underwent clinical neurological examinations with reference to cranial nerves, motor and sensory systems, reflexes, coordination, and gait. Neurophysiological studies performed included electromyography on muscles of the forearm and leg. Nerve stimulation studies were performed with a surface electrode (motor nerve conduction velocity, residual latency).

Effects noted in study and corresponding doses: In the questionnaire, only the prevalence of headaches, dysesthesia of limbs, and muscle weakness was higher in the exposed group compared to the control. Cranial nerve examinations plus motor and sensory nerve examinations did not reveal any objective abnormal neurological signs. Differences (p<0.05) in the jump test (muscle strength) and the tuning fork test (vibration sensation) were noted. A general trend of diminished muscle strength reflexes was found in the biceps and knees of exposed workers; however, statistically, the difference was not significant. Conduction velocities and distal latencies in the control group were similar to those reported in other studies (Goodgold and Eberstein 1983; Johnson et al. 1983). Control motor nerve conduction velocity for the ulnar and median nerves was 57.3 m/sec ±3.4 in this study compared to 56.9 m/sec ±6.7 for the ulnar nerve in a reference group of 101 males (Johnson et al. 1983). Control motor nerve conduction velocity for the posterior tibial nerve was 48.3 m/sec ±2.3 in this study compared to a reference range of 44.8–51.2 m/sec (Goodgold and Eberstein 1983). No significant differences in electromyograms or nerve conduction velocities in the right median or ulnar nerves were found between the control and exposed groups. However, statistical differences (p<0.05) were detected in the posterior tibial nerve. An increased residual latency of motor conduction and a decreased maximal motor nerve conduction velocity were reported in the exposed workers. Residual latency was 2.21±0.34 m/sec in control versus 2.55±0.48 m/sec in exposed subjects; maximal motor nerve conduction velocity was 48.3±2.1 m/sec in controls versus 46.6±2.3 m/sec in exposed subjects. Normal values for the posterior tibial nerve have been reported as 2.1–5.6 m/sec for distal latency and 44.8–51.2 m/sec for conduction velocity (Goodgold and Eberstein 1983). The subjects in

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this study were age matched because these parameters vary with increasing age (conduction velocity decreases and distal latency increases). ATSDR considers these differences to be biologically significant.

		Exposed	**Control**
MMCV	(m/sec)	46.6±2.3*	48.3±2.1
MAP k/a	(%)	90.1±7.4	88.9±11.8
RL	(msec)	2.55±0.48*	2.21±0.34
CVSF	(m/sec)	38.6±2.2	39.1±1.5
dSCV	(m/sec)	42.6±5.0	41.7±3.9
MNCV	(m/sec)	59.1±3.4	60.2±3.3

* significantly different from those of the control group (P<0.05).

CVSF = conduction velocity of slow α = motor fibers; dSCV = distal sensory nerve conduction velocity; MAP k/a = proximal to distal amplitude ratio of muscle action potentials; MMCV = maximal motor nerve conduction velocity; MNCV = mixed nerve conduction velocity; RL = residual latency of motor nerve conduction

Dose end point used for MRL derivation:

[ ] NOAEL [x] LOAEL

Uncertainty factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: Not applicable.

Was a conversion used from intermittent to continuous exposure? If so, explain: According to Veulemans et al. (1982), steady-state conditions for *n*-hexane in blood are achieved by 100 minutes of exposure in humans; thus, it is not appropriate to adjust from intermittent to continuous exposure.

MRL = LOAEL ÷ UF
= 58 ppm ÷100
= 0.58 ppm
= 0.6 ppm

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
Not applicable.

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Other additional studies or pertinent information that lend support to this MRL:
It is not clear whether the acetone co-exposure contributed to the neuropathy observed in this study.
Indirect evidence from an occupational study (Cardona et al.1996) showed that workplace acetone
concentrations had a statistical correlation with the ratio of urinary metabolites to *n*-hexane air
concentration, but not with measured urinary metabolites. No animal studies are available describing the
effects of inhalation co-exposure to acetone and *n*-hexane, although there are several studies which report
interactions between acetone and the neurotoxic metabolite of *n*-hexane 2,5-hexanedione. Oral
administration of acetone has been reported to potentiate the neurotoxicity caused by oral exposure to the
n-hexane metabolite 2,5-hexanedione in rats (Ladefoged et al.1989, 1994). Oral exposure to acetone alone
in rats at 650 mg/kg/day resulted in a statistically significant decrease in motor nerve conduction velocity
after 6 weeks; co-exposure to acetone and 1,300 mg/kg/day 2,5-hexanedione resulted in greater effects than
those seen with 2,5-hexanedione alone (Ladefoged et al.1989). It is possible that acetone may potentiate
n-hexane neurotoxicity by decreasing body clearance of 2,5-hexanedione (Ladefoged and Perbellini 1986).
Simultaneous subcutaneous injection of acetone and 2,5-hexanedione increased the peak concentration of
2,5-hexanedione in rat sciatic nerve compared to injection of 2,5-hexandione alone (Zhao et al.1998).
Acetone also influences the action of many chemicals by its induction of the cytochrome P-450 isozyme
CYP2E1 (Patten et al.1986). *n*-Hexane is metabolized by P-450 isozymes; induction by acetone may
result in an increased production of the neurotoxic metabolite 2,5-hexanedione. The likelihood of
potentiation is small since the equivalent (assuming 100% absorption) of the 650 mg/kg/day acetone used
in the Ladefoged study is

$$\frac{650 \text{ mg/kg/day}}{20 \text{ m}^3/\text{day}} \times 70 \text{ kg} \times \frac{24.45}{56.08} = 957 \text{ ppm},$$

which is quite high compared to the 39 ppm in the Sanagi et al. (1980) study.

If the neurotoxicity of *n*-hexane was potentiated in this study by co-exposure to acetone, the level of
n-hexane alone required to produce these effects would be higher than 58 ppm and the MRL level would be
higher. Results from simulations with a PBPK model that accurately predicted *n*-hexane blood and 2,5-
hexanedione urine levels (Perbellini et al.1986, 1990a) indicate that at concentrations of 50 ppm, the
ratelimiting factor in *n*-hexane metabolism is delivery to the liver, not metabolic activity. This suggests that
at this concentration (and at the MRL concentration of 0.6 ppm), induction of P-450 enzymes in the liver by
acetone or other chemicals would not affect the rate at which 2,5-hexanedione was produced from
n-hexane.

n-Hexane is an aliphatic hydrocarbon present in many industrial solvents. It is highly volatile (vapor
pressure 150 mm Hg at 25 °C) and practically insoluble in water (9.5 mg/L). Brief exposures in humans
to up to 500 ppm are not irritating to the eyes, nose, or throat (Nelson et al.1943). Occupational exposure
to *n*-hexane has caused a peripheral neuropatby (both sensory and motor) in humans (Yamamura 1969).
The clinical course begins with an insidious numbness in the hands and feet followed by muscle weakness
in the extremities. Severe cases result in muscle atrophy and wasting, and sometimes quadriplegia.
Removal from exposure results in recovery in affected individuals, the time to recovery depending on the
severity of the initial condition. The dose-duration relationship for occupational *n*-hexane neuropathy is not
well characterized. Results from a canvass of over 2,000 shoe workers in Japan (93 of whom were
diagnosed with neuropathy) indicated that clinical symptoms resulted after exposure for several months for
8-14 hours a day at air concentrations of 500-2,500 ppm (Yamamura 1969). Effects on motor nerve
conduction velocities, but no clinical symptoms, have been reported in individuals chronically exposed to
195 ppm (Mutti et al.1982b), 69 ppm (Mutti et al.1982a). In these two studies, exposure to methyl ethyl
ketone (which potentiates *n*-hexane in humans and rats [Altenkirch et al.1977, 1982]) also occurred.

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The critical effect for *n*-hexane is neurotoxicity, and the sensitive species is the rat, The EPA used LOAELs from the same study to establish a Reference Concentration (RfC) of 0.2 mg/m^3 (0.06 ppm) for *n*-hexane (IRIS 1996). This was based on a LOAEL of 58 ppm (LOAEL$_{[HEC]}$ 73 mg/m^3) for decreased nerve conduction velocity in humans after occupational exposure for an average of 6.1 years (Sanagi et al. 1980). A supporting study had a LOAEL for respiratory effects of 1,000 ppm (LOAEL$_{[HEC]}$ 77 mg/m^3) in B6C3F$_1$ mice (Dunnick et al.1989). Uncertainty factors were 10 to protect unusually sensitive individuals, 10 for use of a LOAEL rather than a NOAEL, and 3 for both the lack of data on reproductive and chronic respiratory effects. EPA also adjusted from an inhalation rate of 10 m^3/ 8-hour workday to 20 m^3/day and from 5 days/week to 7 days.

Agency Contact (Chemical Manager): Olivia Harris

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)   <u>Route of Exposure</u> 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.

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(2)   <u>Exposure Period</u> 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)   <u>Health Effect</u> 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)   <u>Key to Figure</u> 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)   <u>Species</u> 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)   <u>Exposure Frequency/Duration</u> 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 1 S), 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)   <u>System</u> 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)   <u>NOAEL</u> 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)   <u>LOAEL</u> 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)   <u>Reference</u> The complete reference citation is given in chapter 8 of the profile.

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(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 ope*n*-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]

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

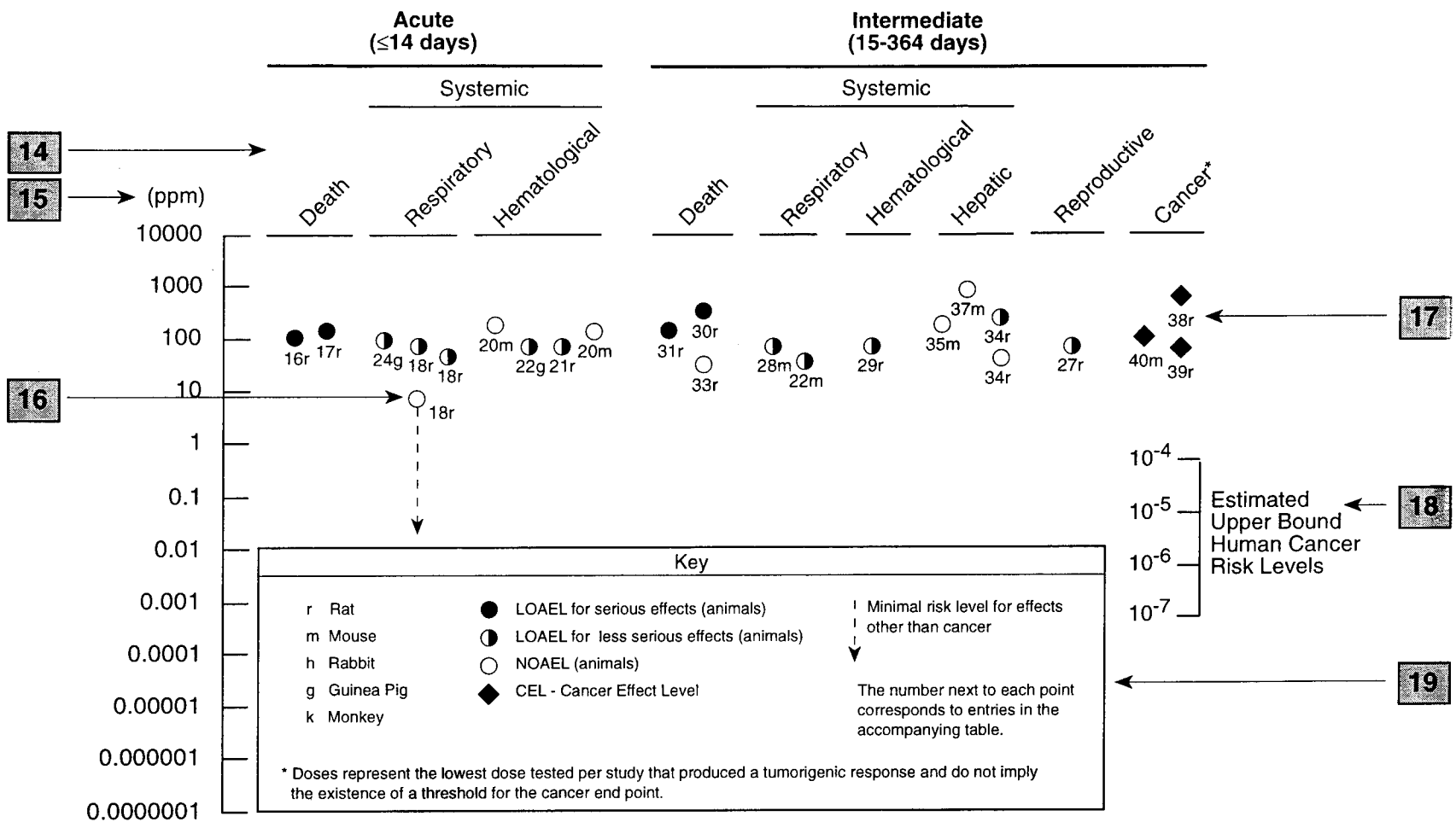| Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
	[5]	[6]	[7]	[8]	[9]		[10]
Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

SAMPLE

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

| Acute (≤14 days) | Intermediate (15-364 days) |

Systemic

Systemic

14 ⟶

15 ⟶ (ppm)

Death Respiratory Hematological Death Respiratory Hematological Hepatic Reproductive Cancer*

10000

1000   ○ (37m)   ◆

100   ● ●   ◑ ◑ ◑   ○ ◑ ◑ ○   ● ●30r   ◑   ◑   ○37m ◑   ◑   ◆38r
16r 17r   24g 18r 18r   20m 22g 21r 20m   31r   28m 22m   29r   35m 34r   27r   40m 39r
    ○33r   ○34r

16 ⟶ 10   ○18r

1

0.1

0.01

0.001 10^{-4}

0.0001 10^{-5} Estimated ⟵ **18**
           Upper Bound
0.00001 10^{-6} Human Cancer
           Risk Levels
0.000001 10^{-7}

0.0000001

17 ⟵ (points to 38r)

Key

r Rat	● LOAEL for serious effects (animals)	‖ Minimal risk level for effects other than cancer	
m Mouse	◑ LOAEL for less serious effects (animals)		
h Rabbit	○ NOAEL (animals)		
g Guinea Pig	◆ CEL - Cancer Effect Level	The number next to each point corresponds to entries in the accompanying table.	
k Monkey			

* 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.

19 ⟶ (points to Key)

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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).

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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/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level

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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

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MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
MCV	motor nerve conduction velocity
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

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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

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>	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