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 clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: November 1998
Profile status: Draft 2 Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 43
Species: Mouse

Minimal Risk Level: 0.5 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Landry DL, Quast JF, Gushow TS, Mattsson. 1985. Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundamental and Applied Toxicology 5:87-98.

Experimental design: An acute MRL of 0.5 ppm was derived from a NOAEL of 50 ppm for no effect on motor coordination or damage to the cerebellar granule cells. Landry et al. (1985) evaluated the neurologic effects of continuous versus intermittent chloromethane exposure in female C57BL/6 mice. Groups of 12 mice each were exposed to chloromethane in whole body inhalation chambers for 11 days either continuously 22 hours/day at 0, 15, 50, 100, 150, 200, or 400 ppm or intermittently 5.5 hours/day at 0, 150, 400, 800, 1,600, or 2,400 ppm. The mice were subjected to neurofunctional testing (ability to stay on a rotating 4 cm diameter rod) on days 4, 8, and 11. Mice were weighed prior to exposure, on exposure days 4 and 8, and at necropsy. Animals were sacrificed at various times during the experiment, and the following tissues were collected, weighed, and prepared for histological evaluation: brain (cerebellum, cerebrum, brain stem), sciatic nerve, vertebral bone with spinal cord, liver, kidneys, and thymus.

Effects noted in study and corresponding doses: The MRL was derived from effects observed in the continuously exposed mice. The 400 ppm exposed mice died or were sacrificed by day 4, and the 200 ppm group by day 5, due to severe toxicity. Mice exposed to 150 ppm were sacrificed in moribund condition by day 10.5. At 200 ppm, the mice were ataxic and fell on their sides after 3 days. At 150 to 400 ppm, the mice developed motor incoordination. Performance on a rotating rod was significantly decreased at 150 ppm and greater. No effects were seen at 50 ppm or below. Histologically, degenerative changes in the cerebellum granule cells were seen at ≥100 ppm, and consisted of nuclear pyknosis and karyorrhexis. At 150 ppm on day 4, there was a moderate intracellular and extracellular cerebellar vacuolation in the Purkinje and/or molecular cell layer and in the white matter. This vacuolation was transient and not seen after day 6 or later. These effects were more pronounced in the 400 ppm mice. Similar effects were seen in mice exposed to higher concentrations intermittently (see separate entries). The apparent greater susceptibility to continuous exposure may be related to the conversion of chloromethane to a toxic metabolite, to decreased respiration at concentrations that are intolerable when exposure is continuous, and/or to diurnal susceptibility.

15 and 50 ppm = No neurologic effects or histopathologic damage observed.

100 ppm = Slight degenerative changes in the cerebellum granule cells with nuclear pyknosis and karyorrhexis.

150 ppm = Moderate cerebellar lesions and severe performance decrement on neuromotor tests.

200 ppm = Incapacitated after 4 days, severe cerebellar lesions.
400 ppm = Incapacitated after 2 days, severe cerebellar lesions.

Dose end ooint used for MRL derivation: 50 ppm; no neurological effects or histopathologic damage observed

[X] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

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

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the acute exposure NOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b).

If an inhalation studv in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$NOAEL_{[HEC]}\ (ppm) = NOAEL_{[ADJ]}\ (ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$

$$= 50\ ppm \times [1] = 50\ ppm$$

where,

$NOAEL_{[HEC]}$ = the NOAEL human equivalent concentration
$NOAEL_{[ADJ]}$ = the NOAEL adjusted for duration
Hb/g = the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A, H = the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL: Neurological effects have been described in numerous case reports of humans exposed to chloromethane vapors as a result of industrial leaks and leaks from defective refrigerators (Baird 1954; Gudmundsson 1977; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). Depending on the extent of exposure and the availability of medical

treatment, the signs and symptoms can range from staggering and blurred vision to coma, convulsions, and death.

Severe neurological signs (ataxia, tremors, limb paralysis, incoordination, convulsions) have been observed in rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed acutely by inhalation to high concentrations of chloromethane (Burek et al. 1981; Chellman et al. 1986a, 1986b; Landry et al. 1985; McKenna et al. 198 la; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have also been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice are more susceptible than rats (Morgan et al. 1982; CIIT 1981), and more sensitive to neurological effects after continuous exposure to low concentrations than after intermittent exposure to higher concentrations of chloromethane (Landry et al. 1985). The greater sensitivity of mice to continuous exposure makes the mouse a good model for the neurotoxicological effects seen in humans.

Agency Contact (Chemical Manager): Alfred Dorsey

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Chloromethane
CAS number(s): 74-87-3
Date: November 1998
Profile status: Draft 2 Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 73
Species: Mouse

Minimal Risk Level: 0.2 [ ] mg/kg/day [Xl ppm [ ] mg/m^3

Reference: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 408120717. Microfiche 511310.

Experimental design: An intermediate MRL of 0.2 ppm (rounded to one significant figure from 0.17) was derived from a LOAEL of 51 ppm for significantly increased serum levels of alanine amino transferase (indicative of hepatotoxicity) in male mice at the 6 month time point in a 2-year study. The objective of the study was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and B6C3F_1 mice. Animals (120 per sex per exposure level) were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to two years. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure (n=10, 10, 20, 80 for rats; and n=10, 10, 10, 90 for mice; respectively). Actual measured concentrations averaged for the 24-month exposure overall were 0.3±4, 51±9, 224±6, and 997±65 ppm. All animals were observed twice daily for signs of toxicity, abnormal behavior, anorexia, or abnormal physical condition. Body weights were collected weekly for 6 months and biweekly thereafter. Ophthalmic exams were performed at baseline and at sacrifice. Prior to the 18- and 24-month sacrifices, neurofunction exams were performed. Blood samples were collected from selected animals at each scheduled necropsy period for hematological and clinical chemistry evaluations; 16-hour urine samples were collected from the same animals for urinalysis. At necropsy, a gross pathology examination was performed, organs (heart, brain, gonads, liver, kidneys, and lungs) were weighed and tissue samples were collected. Histological evaluation of tissues was performed only on tissues collected from the high dose and control animals. Target organ tissues in rats (reproductive tissues, kidney liver, lung) and mice (liver, kidney, spleen) were histologically evaluated in animals of all dose groups.

Effects noted in study and corresponding doses: A dose-response effect for liver toxicity was observed in male mice. Females also had increased ALT, but the increase was not associated with treatment-related histopathological changes in the liver. Liver necrosis and other pathological changes in the liver of high dose male mice was also observed at 12, 18, and 24 months.

51 ppm = Increased ALT levels in male mice; no histopathological changes in the liver.

224 ppm = Increased ALT levels in male mice; no histopathological changes in the liver.

997 ppm = Increased ALT levels; histopathological changes including necrosis, karyomegaly, polykarocytes.

Dose end point used for MRL derivation:51 ppm; increased ALT levels.

[ ] 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)

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the intermediate exposure LOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b). The $LOAEL_{[ADJ]}$ = LOAEL = 51 ppm.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$LOAEL_{[HEC]}\ (ppm) = LOAEL_{[ADJ]}\ (ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$

$$= 51\ ppm \times [1] = 51\ ppm$$

$LOAEL_{[HEC]}$ = the LOAEL human equivalent concentration
$LOAEL_{[ADJ]}$ = the LOAEL adjusted for duration (see above)
Hb/g = the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A H = the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL:
Case reports of humans exposed to chloromethane vapors have described clinical jaundice and cirrhosis of the liver (Kegel et al. 1929; Mackie 1961; Weinstein 1937; Wood 195 l), but exposure concentrations were not known.

Hepatic effects have been observed in animals exposed by inhalation to chloromethane at concentrations >l,000 ppm in acute, intermediate, and chronic duration experiments (Burek et al. 1981; Chellman et al. 1986a; CIIT 1981; Landry et al. 1985; Mitchell et al. 1979; Morgan et al. 1982). Milder liver effects

occurred in mice exposed acutely to an intermittent but relatively high concentration than to a low but continuous concentration (Landry et al. 1985). The greater susceptibility to continuous exposure may result from relatively greater metabolism to a toxic intermediate or from diurnal susceptibility. Hepatic effects were more severe in mice (necrosis and degeneration) than in rats (cloudy swelling, fatty infiltration, increased ALT and AST with no necrosis). Furthermore, no hepatic lesions were observed in rats over the course of 2 years of inhalation exposure to 1,000 ppm, while mice similarly exposed had necrotic lesions after 6 months (CIIT 1981). The greater susceptibility of mice to the hepatotoxic effects of chloromethane may be related to the greater ability of chloromethane to conjugate with hepatic glutathione in mice than in rats (Dodd et al. 1982; Kornbrust and Bus 1984). The reaction of chloromethane with glutathione appears to be toxifying rather than detoxifying (Chellman et al. 1986b). While the exact mechanism for the hepatotoxic effects of chloromethane is unclear, chloromethane can elicit lipid peroxidation as a secondary consequence of depletion of glutathione (Kornbrust and Bus 1984). Comparison of lipid peroxidation in the S-9 fraction from mouse and rat livers revealed much greater lipid peroxidation in mouse liver than in rat liver. The finding that mice exposed to 2,500 ppm chloromethane expired ethane to an extent comparable to that produced by 2 mL/kg carbon tetrachloride, and developed moderate to severe hepatocellular hydropic degeneration provide further evidence that the mechanism of hepatotoxicity may involve lipid peroxidation.

Agency Contact (Chemical Manager): Alfred Dorsey

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): hloromethane
CAS number(s): 74-87-3
Date: November 1998
Profile status: Draft 2 Post-Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 115
Species: Mouse

Minimal Risk Level: 0.05 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride. Unpublished study prepared by Battelle-Columbus Laboratories, Columbus, OH. OTS Submission Document ID 40-8120717. Microfiche 511310.

Experimental design: A chronic MRL of 0.05 ppm (rounded to one significant figure from 0.051) was derived from a LOAEL of 51 ppm for neurological effects (swelling and degeneration of the axons of the spinal cord) in male and female mice at 18 months in a 2-year study. The objective of the study was to evaluate the toxicologic and oncogenic effects of inhaled chloromethane in male and female Fischer 344 rats and $B6C3F_1$ mice. Animals (120 per sex per exposure level) were exposed to chloromethane in whole body inhalation exposure chambers at target concentrations of 0 (control), 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week for up to 2 years. Necropsies were completed at 6, 12, 18, or 24 months after the initial exposure (n=10, 10, 20, 80 for rats; and n=10, 10, 10, 90 for mice; respectively). Actual measured concentrations averaged for the 24-month exposure overall were 0.3±4, 51±9, 224±16, and 997±65 ppm. All animals were observed twice daily for signs of toxicity, abnormal behavior, anorexia, or abnormal physical condition. Body weights were measured weekly for 6 months and biweekly thereafter. Ophthalmic exams were performed at baseline and at sacrifice. Prior to the 18- and 24-month sacrifices, neurofunction exams were performed. Blood samples were collected from selected animals at each scheduled necropsy period for hematological and clinical chemistry evaluations; 16-hour urine samples were collected from the same animals for urinalysis. At necropsy, a gross pathology examination was performed, organs (heart, brain, gonads, liver, kidneys, and lungs) were weighed and tissue samples were collected. Histological evaluation of tissues was performed only on tissues collected from the high dose and control animals. Target organ tissues in rats (reproductive tissues, kidney liver, lung) and mice (liver, kidney, spleen) were histologically evaluated in animals of all dose groups.

Effects noted in study and corresponding doses: There was a consistent dose-response for neurological effects in male and female mice. At the high dose, there was a mild reduction in the number of neurons in the granular cell layer of the cerebellum with decreased width of the granular cell layer. In the high, mid, and low dose groups, axonal swelling and degeneration of minimal severity was observed in the spinal nerves and the cauda equina associated with the lumbar spinal cord.

51 ppm = Swelling and degeneration of axons in the spinal cord.

224 ppm = Swelling and degeneration of axons in the spinal cord.

997 ppm = Tremor, paralysis, mild reduction in the number of cerebellar neurons in the granular cell layer.

Dose end point used for MRL derivation:51 ppm; axonal swelling and slight degeneration of axons in the spinal cord

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

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

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: No adjustment made for the chronic exposure LOAEL. Chloromethane is readily absorbed from the lungs in humans and animals and rapidly (within 1 hour) reaches equilibrium with levels in blood and expired air approximately proportional to the exposure concentrations (Landry et al. 1983a, 1983b; Nolan et al. 1985; Putz-Andersen et al. 1981a, 1981b).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The human equivalent dose (HEC) was calculated using Formula 4-48a from Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b). Though chloromethane is a category 2 gas, the formula in the EPA 1994b document for extrarespiratory effects of category 2 gases is presently under review and the recommended equation is that for category 3 gases:

$$LOAEL_{[HEC]}\ (ppm) = LOAEL_{[ADJ]}\ (ppm) \times \frac{(Hb/g)_A}{(Hb/g)_H}$$

$$= 51\ ppm\ x\ [1] = 51\ ppm$$

where,

$LOAEL_{[HEC]}$	=	the LOAEL human equivalent concentration
$LOAEL_{[ADJ]}$	=	the LOAEL adjusted for duration (see above)
Hb/g	=	the blood:gas (air) partition coefficient [the default value of 1.0 is used for the ratio of (Hb/g),/(Hb/g), if these partition coefficients are not known]
A,H	=	the subscripts A and H refer to animal and human, respectively.

Additional studies or pertinent information that lend support to this MRL: Neurological effects have been described in numerous case reports of humans exposed to chloromethane vapors as a result of industrial

leaks and leaks from defective home refrigerators (Baird 1954; Hansen et al. 1953; Hartman et al. 1955; Kegel et al. 1929; MacDonald 1964; McNally 1946; Jones 1942; Raalte and van Velzen 1945; Spevak et al. 1976; Wood 1951). Depending on the extent of exposure and the availability of medical treatment, the signs and symptoms can range from staggering and blurred vision to coma, convulsions, and death.

Severe neurological signs (ataxia, tremors, limb paralysis, incoordination, convulsions) have been observed in rats, mice, rabbits, guinea pigs, dogs, cats, and monkeys exposed acutely by inhalation to high concentrations of chloromethane (Burek et al. 1981; Chellman et al. 1986a, 1986b; Landry et al. 1985; McKenna et al. 1981a; Morgan et al. 1982; Smith and von Oettingen 1947b). Cerebellar lesions have also been observed microscopically in guinea pigs and rats (Kolkmann and Volk 1975; Morgan et al. 1982). Mice are more susceptible than rats (Morgan et al. 1982; CIIT 1981), and more sensitive to neurological effects after continuous exposure to low concentrations than after intermittent exposure to higher concentrations of chloromethane (Landry et al. 1985). The greater sensitivity of mice to continuous exposure makes the mouse a good model for the neurotoxicological effects seen in humans.

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

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

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

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

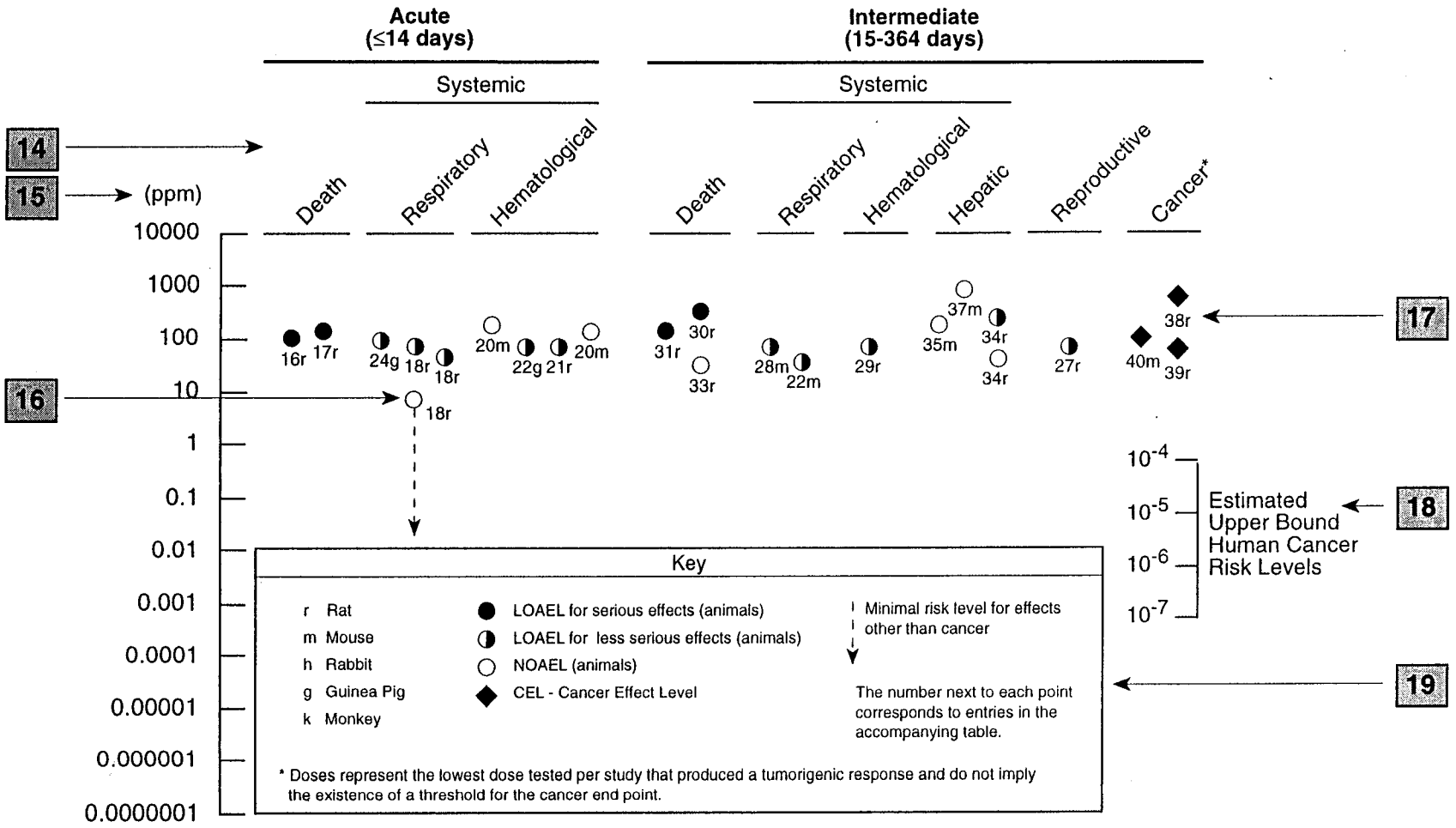
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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



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

APPENDIX C

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

APPENDIX C

$<$	less than
$\leq$	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

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