APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

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

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

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

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Methylene Chloride
CAS number(s): 75-09-2
Date: July 28, 2000
Profile status: Draft 3 Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 15
Species: Human

MRL: 0.6 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Winneke G. 1974. Behavioral effects of methylene chloride and carbon monoxide as assessed by sensory and psychomotor performance. In: Behavioral Toxicology. Early Detection of Occupational Hazards, Eds. C Xintaras, B Johnson, I deGroot. U.S. Department of Health, Education, and Welfare.

Reitz RH, Hays SM, Gargas ML. 1997. Assessing priority data needs for methylene chloride with physiologically-based pharmacokinetic modeling. Halogenated Solvents Industry Alliance (HSIA), prepared for ATSDR.

Experimental design: Winneke (1974) exposed from 6 to 20 volunteers in a randomized blind clinical chamber experiment to either filtered air or to concentrations of 300, 500, or 800 ppm of methylene chloride vapors. Subjects were exposed for 3–4 hours and tested at 45-minute intervals with standard neurobehavioral tests measuring: (1) critical flicker fusion frequency (visual); (2) auditory vigilance performance; and (3) performance on psychomotor tasks.

Effects noted in study and corresponding doses: A statistically significant depression in critical flicker fusion frequency (CFF frequency) was observed at all concentrations. The magnitude of CFF depression was similar at exposure concentrations of 300 and 500 ppm and was larger at 800 ppm. Thus, there was no dose-response at the two lowest concentrations, and a dose-response was evident at the highest concentration. A decrease in auditory vigilance performance was observed at 500 ppm and psychomotor task performance was impaired at 800 ppm. Thus, of the neurological indicators tested, CFF frequency is most sensitive to acute inhalation exposure to methylene chloride. Based on this end point, the LOAEL is 300 ppm.

The Reitz et al. (1997) PBPK model was used to convert the LOAEL to account for a 24-hour exposure scenario, yielding a duration-adjusted LOAEL of 60 ppm.

Dose and end point used for MRL derivation: 60 ppm; the MRL was derived based on a LOAEL of 300 ppm for adverse neurological effects (decreased critical flicker frequency and auditory vigilance performance), duration-adjusted to 60 ppm by Rietz et al. (1997) .

[ ] 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?
No

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

Was a conversion used from intermittent to continuous exposure? If so, explain:
The Reitz et al. (1997) PBPK model was used to convert the LOAEL of 300 ppm to 60 ppm to account for a 24-hour scenario.

Other additional studies or pertinent information that lend support to this MRL: Fodor and Winneke (1971) observed similar effects on critical flicker fusion frequency at the same concentration (300 ppm) in a different group of volunteers. Stewart et al. (1972) observed altered visual evoked responses in humans exposed to 515 ppm methylene chloride for 1–2 hours. Putz et al. (1979) reported impairment in some visual and psychomotor tasks following 4 hours of exposure to 200 ppm of methylene chloride. (Although Putz et al. (1979) identified a lower LOAEL, it was not chosen as the basis for the acute inhalation MRL because ATSDR considered the neurological tests employed by Winneke (1974) to be more specific.) OSHA's (OSHA 1997) new occupational standard of 125 ppm as a 15-minute STEL (short term exposure limit) is consistent with this inhalation MRL.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Methylene Chloride
CAS number(s): 75-09-2
Date: July 28, 2000
Profile status: Draft 3 Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 36r
Species: Rat

MRL: 0.3 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Haun CC, Vernot EH, Darmer KI, et al. 1972. Continuous animal exposure to low levels of dichloromethane. AMRL-TR-72-130, paper no. 12.

Experimental design: Groups of 20 rats (sex and strain not specified) were exposed to methylene chloride vapors continuously for 14 weeks at chamber concentrations of either 0 (controls), 25, or 100 ppm. Body weights and clinical signs were monitored throughout the study. Necropsy was performed and tissues were examined histopathologically and relative organ weights were determined at the end of exposure. The study also evaluated mice, monkeys, and dogs. Those results are described below as supporting evidence.

Effects noted in study and corresponding dose: Cytoplasmic vacuolization and positive-oil-red stain (indicative of fatty infiltration) were reported at 25 and 100 ppm. Nonspecific tubular degeneration and regenerative changes of the kidney were also observed at both exposure levels. The study did not report whether there were exposure-related differences in the incidence or severity of effects. There were no exposure-related effects on organ weights.

Dose and end point used for MRL derivation: The MRL was derived based on a LOAEL of 25 ppm for hepatic effects (cytoplasmic vacuolization and fatty infiltration).

[ ] NOAEL [X] LOAEL:

Uncertainty factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a minimal LOAEL)
[ ] 1 [X] 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?
No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
The blood:gas partition coefficient ($H_{b/g}$) for the Sprague-Dawley rat and human are 19.4 and 8.94, respectively. The ratio of the rat $H_{b/g}$ to the human $H_{b/g}$ is:

$(H_{b/g})_A/(H_{b/g})_H = 19.4/8.94 = 2.2$
Since the ratio is greater than 1, a value of 1.0 was used (EPA, 1994).
$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g})_A/(H_{b/g})_H$

= 25 x 1.0
= 25 ppm

Was a conversion used from intermittent to continuous exposure? If so, explain:
No. Dosing was continuous for 90 days.

Other additional studies or pertinent information that lend support to this MRL: Haun et al. (1972) also evaluated the effects of methylene chloride in mice, dogs, and monkeys. For all three species, exposure was continuous for 14 weeks to 0, 25, or 100 ppm of methylene chloride.

In mice (20/group, sex and strain not reported), exposure to 100 ppm methylene chloride significantly decreased the activity of liver cytochrome P-450 and decreased b_5 at 30, 60, and 90 days. Cytochromes b_5 and P-420 were also reduced at 30 days, but were elevated at 90 days. The 25 ppm exposure level had no significant effect on liver cytochrome activities. Hexobarbital sleeping time measured at 30, 60, and 90 days was not significantly altered by exposure to methylene chloride. Although the authors indicate that at the end of the exposure period, the animals were killed and subjected to gross and histopathologic examination, the only result reported is that mice exposed to 25 ppm of methylene chloride showed no pathologic changes, although the livers of the animals in the 100 ppm exposure group did show positive fat stains.

Four monkeys per exposure level (sex and strain not reported) were exposed to methylene chloride. Hematologic and clinical chemistry tests were conducted at various times during the experiment. Gross and histopathologic examinations were done at the end of the study, but the scope was not indicated (it is assumed that at least the liver and kidneys were examined). Significant but non-toxic elevations in carboxyhemoglobin were seen throughout the study. Carboxyhemoglobin rose from about 0.5% in controls to 1.7 and 4.5% in the low- and high-exposure groups, respectively. Hematology and clinical chemistry values showed no significant differences from controls. The authors also reported that exposure to methylene chloride did not cause any significant gross or histopathologic alterations.

The protocol used with the monkeys was also used with dogs. Sixteen dogs per exposure level were used (sex and strain not reported). Hematology and clinical chemistry results showed no significant differences from control dogs and there were no exposure-related gross or histopathologic alterations.

One additional study that reported effects at similar exposure levels as those as those used by Haun et al. (1972) is that of Kjellstrand et al. (1986) who observed fatty infiltration and increased liver weight in mice exposed continuously to 75 ppm of methylene chloride (the lowest level tested) for 90 days.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Methylene Chloride
CAS number(s): 75-09-2
Date: July 28, 2000
Profile status: Draft 3 Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 63r
Species: Rat

MRL: 0.3 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Nitschke KD, Burek JD, Bell TJ, et al. 1988a. Methylene Chloride: A 2-year inhalation toxicity and oncogenicity study in rats. Fundam Appl Toxicol 11:60-67.

Experimental design: The goal of the Nitchke et al. (1988a) study was to investigate the toxicity of inhaled methylene chloride at lower concentrations than those in the other bioassays, in order to determine a NOAEL for both toxicity and carcinogenicity. Exposure concentrations of 0, 50, 200, and 500 ppm of methylene chloride were selected for this bioassay. Groups of 90 male and 108 female Sprague-Dawley rats were exposed to these concentrations for 6 hours/day, 5 days/week for 2 years. A number of satellite groups were also exposed to assess the temporal relationship between methylene chloride exposure and the expression of toxicity; subgroups of females in the main study were sacrificed after 6, 12, 15, and 18 months of methylene chloride exposure. End points evaluated included: body weight, food consumption rates, organ weights; hematology, clinical chemistry, urinalysis; pathology; histopathology; and blood carboxyhemoglobin levels.

Effects noted in study and corresponding doses: No exposure-related gross or histopathologic changes were observed in animals from interim sacrifice groups. At terminal sacrifice, the incidences of both hepatocellular cytoplasmic vacuolization consistent with fatty changes and multinuceated hepatocytes were statistically elevated in female rats exposed to 200 and 500 ppm of methylene chloride; a slight increase in the incidence of hepatocellular vacuolization was also observed in male rats exposed to 500 ppm. Histopathological changes in the liver were not found in the male rats exposed to 50 or 200 ppm of methylene chloride. No other pathologic or histopathologic nontumor findings were reported.

Dose and end point used for MRL derivation: Based on liver histopathology in female rats, a NOAEL of 50 ppm is used for MRL derivation.

[X] NOAEL [ ] LOAEL:

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [X] 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?
No

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

The blood:gas partition coefficient ($H_{b/g}$) for the Sprague-Dawley rat and human are 19.4 and 8.94, respectively. The ratio of the rat $H_{b/g}$ to the human $H_{b/g}$ is:

$(H_{b/g})_A/(H_{b/g})_H = 19.4/8.94 = 2.2$
Since the ratio is greater than 1, a value of 1.0 was used (EPA, 1994).

$NOAEL_{[HEC]} = NOAEL_{[ADJ]} \times (H_{b/g})_A/(H_{b/g})_H$
$= 8.92 \times 1.0$
$= 8.92$ ppm

Was a conversion used from intermittent to continuous exposure? If so, explain:
Yes. The NOAEL was multiplied by 6/24 hours and 5/7 days.

$NOAEL_{[ADJ]} = 50 \text{ ppm} \times 6/24 \times 5/7 = 8.92 \text{ ppm}$

Other additional studies or pertinent information that lend support to this MRL: The results of this study are consistent with the body of data on methylene chloride toxicity and toxicokinetics. Studies by Burek et al. (1984) and NTP (1986) demonstrate concordance and complementarity with the Nitschke et al. (1988a) study. At doses of 500 ppm or higher, these other studies show a clear dose-response with liver histopathology as the end point in rats. The findings of the Nitschke et al. (1988a) bioassay are also supported by what is known about the toxicokinetics and mechanisms of action of methylene chloride toxicity (and carcinogenicity).

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Methylene Chloride
CAS number(s): 75-09-2
Date: July 28, 2000
Profile status: Draft 3 Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 6
Species: Human

MRL: 0.2 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Reitz RH, Hays SM, and Gargas ML. 1997. Assessing Priority Data Needs for Methylene Chloride with Physiologically-Based Pharmacokinetic Modeling. Halogenated Solvents Industry Alliance (HSIA), prepared for ATSDR, using human volunteer data from Winneke (1974).

Experimental design: Reitz et al. (1997) modeled inhalation data from Winneke (1974) to predict the unit concentration of methylene chloride in drinking water needed to produce a tissue-specific dose equivalent to that produced by inhaling 300 ppm of methylene chloride. Volunteers were exposed via inhalation to 300-800 ppm of methylene chloride for approximately 4 hours and tested for neurobehavioral effects that would reflect cortical function.

Reitz et al. (1997) modified the basic PBPK methylene chloride model developed by Andersen et al. (1987), Reitz et al. (1988), and Andersen et al. (1992) in the following manner: (1) liver weights for rodents were based on the actual organ weights of conrol laboratory animals which were sacrificed during chronic toxicity studies at 6–18 months of age; (2) partition coefficients for methylene chloride derived from *in vitro* experiments performed by Gargas et al. (1989), were used for liver, fat, muscle, and blood; and (3) a brain compartment was added to the methylene chloride model so that central nervous system effects could be assessed in female and male rodents and humans. Size of rodent brains, blood flow rates to the brain, and partition coefficients for brain tissue were obtained from either published literature (e.g., Stott et al. 1983; Thomas 1975) or personal communication from the authors. The modified methylene chloride model thus contained six tissue compartments: fat, muscle (slowly perfused tissue), rapidly perfused tissue, liver, mammary tissue, and brain.

Effects noted in study and corresponding doses: Minimally adverse, dose-dependent effects in neurobehavioral measurements were observed (visual critical flicker fusion frequency, auditory vigilance performance, psychomotor tasks). Because similar exposures to 50–100 pm of carbon monoxide alone did not produce these effects, the author (Winneke 1974) concluded that they were mediated by methylene chloride directly and not by its oxidative metabolite carbon monoxide. A LOAEL of 300 ppm from this study, based on decreased visual critical flicker fusion frequency, was used for the derivation of the acute oral MRL. Auditory vigilance and psychomotor performance were only statistically decreased at 500 and 800 ppm, respectively. Thus, critical flicker fusion frequency is the most sensitive end point tested and can be considered to be a minimal effect.

Dose and end point used for MRL derivation: 16 mg/kg/day; route-to-route extrapolation. Reitz et al. (1997) modeled the Winneke (1974) data to obtain the target organ (brain) concentrations of methylene chloride associated with administered inhalation concentrations, and then calculate the human drinking water concentrations (mg/L) that would result in the equivalent target organ-specific doses. Human exposure patterns in the PBPK model simulated realistic human drinking water consumption patterns (i.e.,

consisting of bouts of drinking during the day, with and between meals, and little-to-no drinking during the night). PBPK modeling predicted that peak concentrations of methylene chloride in the brain would increase rapidly after each episode of drinking water consumption, and then drop sharply, to near-zero, between bouts of dringing. Additionally, there would be no cumulative effects of repeated exposure.

For acute neurological effects, the associated dose measure was defined as the peak concentration of methylene chloride in brain tissue (mg/L of brain tissue) of humans exposed to 300 ppm of methylene chloride for 4 hours by inhalation. The modified PBPK model calculated that the administered inhalation dose was equivalent to 3.95 mg of methylene chloride per liter of brain tissue. The equivalent administered human concentration in drinking water that will produce the same neurological effects was 565 mg of methylene chloride/liter. Using a daily drinking water consumption value of 2 liters and an average human body weight of 70 kg, the LOAEL was calculated to be 16 mg/kg/day.

[ ] 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:
Yes. The PBPK model predicted a unit concentration in drinking water in mg/L. This value was multiplied by 2 liters (default drinking water consumption rate) and divided by 70 kg (default human body weight) to yield a mg/kg body weight dose.

Calculated LOAEL = unit concentration (mg/L) x water consumption (L) ÷ BW
= 565 mg/L x 2 L ÷ 70 kg
= 16 mg/kg/day

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

Was a conversion used from intermittent to continuous exposure? If so, explain:
No.

Other additional studies or pertinent information that lend support to this MRL: The PBPK model has been validated.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Methylene Chloride
CAS number(s): 75-09-2
Date: July 28, 2000
Profile status: Draft 3 Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 11r
Species: Rat

MRL: 0.06 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Serota D, Thakur, AK, Ulland BM, et al. 1986a. A two year drinking water study of dichloromethane in rodents. I. Rats. Food Chem Toxicol 24:951-958.

Experimental design: Only one long-term bioassay has been conducted with methylene chloride (Serota et al. 1986a, 1986b). Fischer-344 rats (85/sex/dose) and $B6C3F_1$ mice (50–200/sex/dose) were exposed to methylene chloride in deionized drinking water at target concentrations aimed at exposing rats to 0, 5, 50, 125, or 250 mg/kg/day and mice to 0, 60, 125, 185, and 250 mg/kg/day for 104 weeks. Two untreated control groups were run concurrently. The nominal mean doses were 0, 6, 55, 131, and 249 mg/kg/day. A satellite group was exposed to nominal daily doses of 250 mg/kg/day for 78 weeks followed by a 24-week recovery period. Subgroups of animals were sacrificed at 26, 52, and 78 weeks in treated groups and one control group. Body weights and food and water consumption rates were recorded weekly. Ophthalmologic examinations were conducted prior to treatment and at termination of treatment. Hematology, serum chemistry, and urinalysis assessments were done during interim sacrifices at 52 and 78 weeks. Organ weights were evaluated and all animals received a complete necropsy.

Effects noted in study and corresponding doses: At the two highest dose groups, the following findings were observed in rats: decreased body weights and body weight gains in both sexes, with concomitant decrease in water consumption throughout the study and in food consumption during the first 13 weeks, and changes in hematology and serum chemistry, but not urinalysis parameters. No treatment-related ophthalmologic effects were observed throughout the study. Gross pathological effects were unremarkable. There were no histopathologic changes except in the liver. A dose-related, statistically significant, positive trend in the incidences of hepatic foci, areas of cellular alterations, and fatty deposits were observed in all dose groups, but the lowest occurred at both week 78 and week 104. After 24 weeks of nontreatment, the fatty deposits in the recovery group decreased, but there was no change in the incidence of cellular foci or areas of cellular alterations.

In mice (Serota et al. 1986b), the liver was the only identifiable target organ. There was a marginal increase in the fatty content of the liver in the highest dose group, although the significance of this finding was not clear.

Dose and end point used for MRL derivation: 6 mg/kg/day. Histopathology was only observed in the liver; therefore, the liver is the critical target organ. Marginal liver changes were only observed in mice at the highest dose level tested. Statistically significant cellular changes (hepatic foci, areas of cellular alterations) were observed in all dose groups in the rat except for the lowest. Therefore, the lowest dose in the rat study was identified as the NOAEL. Based on measured mean drinking water consumption rates, this dose was calculated to be 6 mg/kg/day.

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

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

Was a conversion used from intermittent to continuous exposure? If so, explain:
No.

Other additional studies or pertinent information that lend support to this MRL: These data are consistent with the large body of data on methylene chloride toxicity and toxicokinetics.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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

LEGEND

See LSE Table 2-1

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

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

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

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

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

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

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

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

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

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

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious

effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

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

SAMPLE

1 6

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

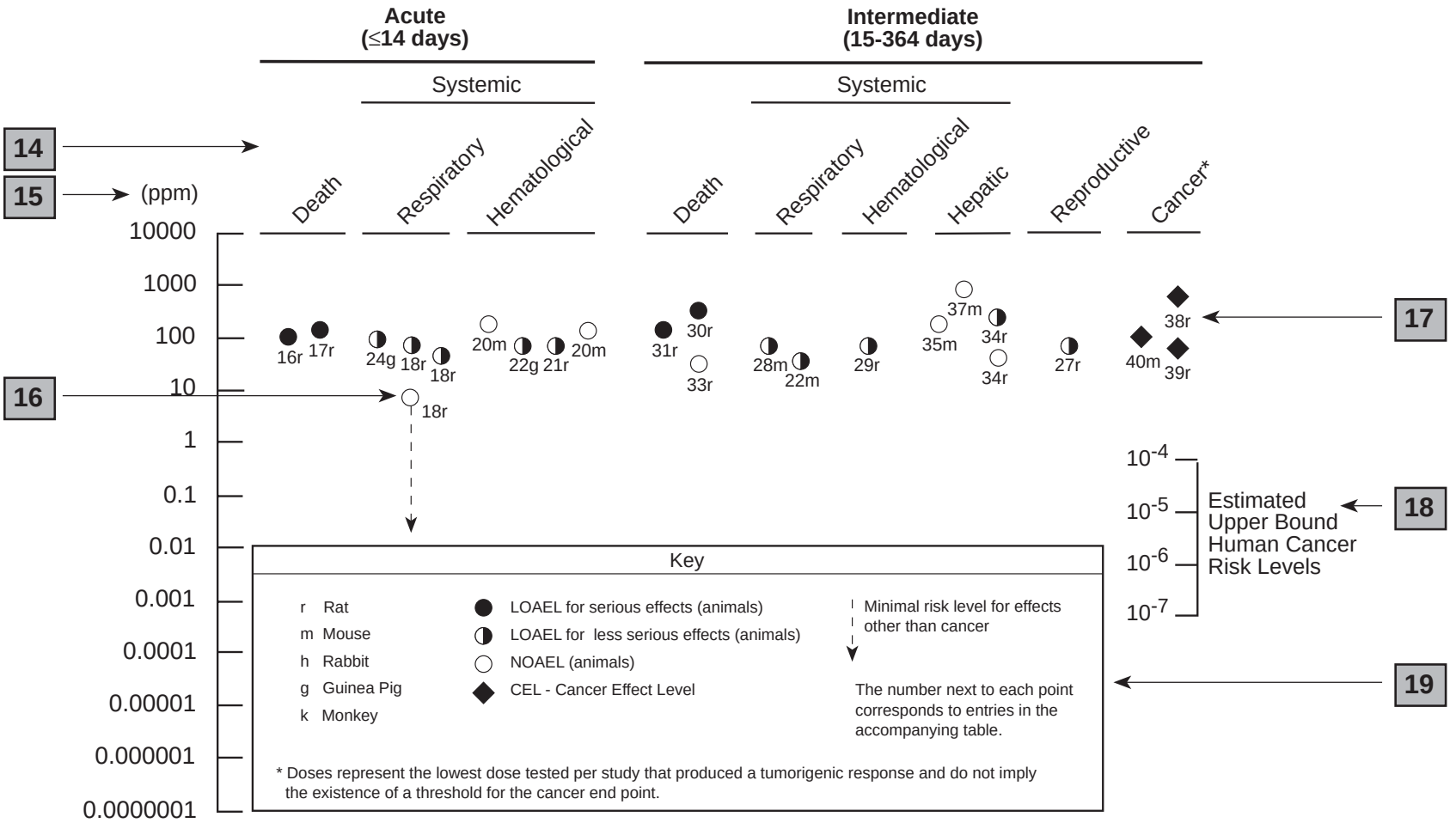
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

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

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

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).

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
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
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
CHO/HPRT	Chinese Hamster ovary assay involving the hypoxanthine guanine phosphoribosyl transferase gene
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
COHb	carboxyhemoglobin
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
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBPK	physiologically-based pharmacokinetic
PEL	permissible exposure limit
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
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