APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived-for acute (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 chemicalinduced 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.

APPENDIX A

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/MR.L 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) WORKSHEETS

Chemical name:	1,6-Hexamethylene Diisocyanate
CAS number:	822-06-0
Date:	February 25, 1998
Profile status:	Second Draft
Route:	[X] Inhalation [ ] Oral
Duration:	[ ] Acute [X]Intermediate [ ] Chronic
Key to figure:	19
Species:	Sprague-Dawley rat

MRL: 3.0×10^{-5} [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Mobay Corporation 1984

Experimental design: The purpose of this study was to determine the toxicity of HDI via inhalation exposures over a 3-week period in Sprague-Dawley rats. Groups of 10 male and 10 female rats were exposed (head-only) to vapors of HDI at average concentrations of 0, 0.005, 0.0175, 0.15, or 0.3 ppm for 5 hours/day, 5 days/week for 3 weeks. Five animals per sex per exposure concentration were sacrificed at the end of the exposure period; the balance of the animals were allowed a 2-week period to recover from the exposures and then sacrificed. Hematology, blood chemistry, gross necropsy, and histopathology were conducted on all animals, as well as urinalysis (UA), body weight measurements and feed consumption.

Effects noted in study and corresponding doses: All animals exposed to all concentrations of HDI exhibited varying degrees of irritation of eyes and/or noses during exposure and at 1 hour postexposure, with all animals appearing normal the following morning. No clinical signs of toxicity were observed during the non-exposure days (i.e., weekends). All animals exposed to 0.15 ppm were sneezing during the last week of exposure while the animals exposed to 0.3 ppm started to sneeze at the end of the first week of exposure and then sneezed randomly during the second and third week of exposure. Sneezing was attributed to irritation of the nasal cavity. All animals in the control group showed slightly irritated eyes and/or noses at 1 hour postexposure and appeared normal at all other times. The severity of the irritation in the animals exposed to the 0.005 ppm level was mild and appeared to be slightly above that of controls. No significant differences in body weights, feed consumption, blood chemistry, UA and hematology were observed compared to control animals for both male and female rats. At an HDI exposure concentration of 0.3 ppm, a statistically significant decrease in liver and kidney absolute and relative weights of female rats only was observed in those animals sacrificed immediately after the 3-week exposure was completed. Male rats exposed to 0.3 ppm HDI showed a significant decrease in the relative and absolute kidney weights, but not for liver weights. No other statistically significant changes in organ weights were observed at any of the lower inhalation doses of HDI. No significant changes in gross pathology of any of the other body organs were found. Microscopic changes in the nasal cavity, trachea and larynx were noted. Changes in the nasal tract included hemorrhage, inflammatory exudate and epithelial changes; the epithelial changes varied from vacuolation and disruption of epithelial cells to a more chronic squamous metaplasia, characterized by a loss of cilia and change from the normal ciliated pseudostratified columna to a more flattened squamous type epithelium with minimal to mild keratinization. Changes in the larynx included focal accumulations of inflammatory cells in the submucosa and a minimal to mild hyperplasia of the epithelium. The nasal changes occurred in a dose-related manner. At 0.3 ppm, 80–90% of the animals were affected with moderate severity as described above, while at 0.15 ppm, 50–70% were affected with a slightly milder severity. At 0.005 ppm and

0.0175 ppm, the changes were minimal to mild in severity and were similar to controls even though the incidence was slightly higher in the 0.0175 ppm males. The severity of the changes in the trachea and larynx were not dose related.

The dose response effects reported in this study are summarized below:

0.3 ppm: Nasal epithelial changes in 80–90% of animals; moderate severity. No observed effects were noted for the following systems: cardiac, gastrointestinal, hematological, musculoskeletal, hepatic (males only), endocrine, dermal, immunological/lymphoreticular, neurological, reproductive and body weight (NOAELs). Decreased kidney weights (males and females) and decreased liver weights (females only) were also noted (both are less serious LOAELs).

0.15 ppm: Nasal epithelial changes in 50–70% of animals at slightly milder severity. No observed adverse hepatic effects (females only) and no observed adverse renal effects (males and females).

0.0175 ppm: Minimal LOAEL. Hemorrhage, inflammatory exudate, epithelial changes in nasal cavity.

0.005 ppm: NOAEL.

Dose end point used for MRL derivation:

[X] NOAEL [ ]LOAEL

Uncertainty factors used in MRL derivation:

[X] 1 [ ] 3 [ ] 10 (for use of a NOAEL)
[ ] 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?
If so, explain:

No.

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

The NOAEL Human Equivalent Dose ($NOAEL_{HEC}$) was calculated using Equation 4-16 from EPA (1994):

$$NOAEL_{HEC} = NOAEL \times RGDR_r$$

where $RGDR_r$ is the Regional Gas Dose Ratio for the region of interest. For HDI, the region of interest for this exposure route and duration for the rat is the nasal cavity. Again using EPA (1994) guidance and the dose-response relationships observed in rats outlined above, HDI effects would be classified as extrathoracic. HDI is also classified as a Category 1 gas (see pages 3–38 and 3–39 of EPA 1994), hence, Equation 4-18 of EPA (1994) was used to calculate the $RGDR_{ET}$.

$$NOAEL_{[HEC]} = NOAEL \times RGDR_{ET}$$

$$NOAEL_{[HEC]} = (0.005 \text{ ppm}) \times (V_E/SA_{ET})_A / (V_E/SA_{ET})_H$$

$NOAEL_{[HEC]}$ = 0.005 ppm x (0.24 m^3/day / 11.6 cm^2) / 20 m^3/day / 177 cm^2)

$NOAEL_{[HEC]}$ = 0.005 ppm x 0.183

$NOAEL_{[HEC]}$ = 0.0009 ppm

Therefore:

MRL = $NOAEL_{[HEC]}$ / UF

MRL = 0.0009 ppm/ 30

MRL = 3.0 x 10^{-5} ppm

where the $NOAEL_{[HEC]}$ is the Human Equivalent Concentration for the no-observed-adverse-effect level, the RGDR is the Regional Gas Dose Ratio (animal (A): human (H)), V_E is the ventilation volume (tidal volume in m^3/day) , SA is the regional surface area of the toxic effect observed (in cm^2), and UF are the uncertainty factors.

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:

Similar nasal lesions were reported in another study of intermediate duration (Mobay Corporation 1988); however the lowest air concentration found that induced a LOAEL (ocular irritation and lacrimation) was twice the LOAEL for the Mobay Corporation study. In support of the 0.005 ppm NOAEL in rats, a study by Shepperly and Hathaway (1991) reported a NOAEL for workers exposed to HDI at concentrations of 5 ppb (0.005 ppm) or less at a plant in Freeport, Texas. These workers had been chronically exposed to HDI for >1 year with no statistically significant differences in pulmonary function test data, nor any significant increase in the frequency of respiratory complaints observed in these exposed workers versus the control (unexposed) population. A later study by DeWilde and Hathaway (1994), again using chronically exposed workers at the Freeport, Texas plant, found no statistically significant differences in pulmonary function data among HDI exposed individuals and the control group. The dose in that study was estimated to be between 0.5 and 7 ppb (0.0005–0.007 ppm). Both the Shepperly and Hathaway (1991) and the DeWilde and Hathaway (1994) studies provided estimates of HDI doses to which the workers were exposed, but neither study could provide definitive exposure doses to the worker populations. Both studies also had difficulties with some of the industrial hygiene monitoring devices and personal dosimetry devices, which may have provided inaccurate exposure data. In addition to occasional high short-term exposures (10–20 ppb), there were also some large variations in pulmonary function test results, which varied markedly from year to year and were attributed to human error. These study limitations precluded either of these reports from being used to derive an intermediate-duration MRL based on human exposures, but they do lend some support to the MRL based on results found using the rat model.

Agency Contact (Chemical Manager): Henry Abadin

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name: 1,6-Hexamethylene Diisocyanate
CAS number: 822-06-0
Date: February 25, 1998
Profile status: Second Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 32
Species: Fischer 344 rat

MRL: $1.0x10^{-5}$ [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Mobay Corporation 1989

Experimental design: The purpose of this study was to provide information on the NOAEL/LOAEL and the toxic and oncogenic effects associated with exposure of rats to HDI by the inhalation route over a period of 2 years. Groups of 60 male and 60 female Fischer 344 rats were exposed to 0, 0.005, 0.025, or 0.175 ppm HDI for 5 days/week, 6 hours/day for 2 years. Control rats were sham exposed rats (conditioned air exposure). HDI vapor concentrations were generated by passing filtered, dry air through liquid HDI in a glass bubbler immersed in a heated water bath, with the temperature of the bath altered to affect the concentration of HDI needed for exposure. Animals were monitored for clinical signs of toxicity, ophthalmological examinations, body weight changes, organ weight changes (at gross necropsy), and changes in hematologic, urine and blood chemistry parameters during the course of the study.

Effects noted in study and corresponding doses: HDI caused eye irritation in males exposed to the 0.175 ppm dose only during the first year of the study and not during the second year. No other HDI-related eye lesions were detected during ophthalmologic examinations performed during the 2-year study. Decreases in body weight (compared to control animals) were small (only a 5% decrease) but consistent, and were considered to be related to the toxicity of HDI in female rats exposed to the 0.175 ppm dose during the second year of the study only. There were also no statistically significant differences in terminal body weight between controls and exposed male rats at the end of the study. Hematologically, the only effect that HDI may have had was an increase in the number of reticulocytes at different intervals during the study in both males and females exposed to the 0.175 ppm concentration of HDI, suggesting anemia. No statistically significant HDI exposure-related changes in serum chemistry and urinalysis were noted. At gross necropsy, many non-HDI body organ changes were noted; however, there were increases in the relative brain, heart, lung, and spleen weights in the 0.175 ppm HDI-treated females, with an increase in absolute spleen weight in this group as well. Although these organs had increased weight compared to controls, the values were still within accepted control range values and not considered an effect of HDI inhalation exposure. HDI-related histopathological changes were limited to the nasal cavity and lungs. Lung lesions included epithelialization, interstitial pneumonia or alveolar macrophage accumulation in both sexes in the 0.025 and 0.175 ppm exposure groups, but not at the 0.005 ppm dose level. Histopathological lesions within the nasal cavity were numerous; however, only a few were considered to be a direct effect of HDI inhalation exposure. The 0.175 ppm exposure group lesions included degeneration of the olfactory epithelium, hyperkeratosis, occasional atrophy, and focal erosion or ulceration of the olfactory epithelium, with these lesions not present in the lowest (0.005 ppm) exposure group. Other lesions in the nasal cavity that occurred due to HDI exposure in the 0.025 and 0.005 ppm exposure groups include hyperplasia/metaplasia, mucus hyperplasia, and inflammation. Combining information obtained from a satellite group of rats exposed to HDI at identical

concentrations, it was found that after 1 year of exposure, an adaptive nasal epithelial response (mucus secretory cell and epithelial hyperplasia) was observed at the lowest dose (0.005 ppm). At the 0.025 and 0.175 ppm concentrations, a progression from this response occurred, exhibited as hyaline droplet degeneration, hyperkeratosis, chronic inflammation and olfactory epithelial damage. After 2 years of exposure, an adaptive response at the lowest concentration occurred, characterized by hyperplasia/metaplasia and hyaline droplet degeneration. At the 0.025 and 0.175 ppm concentrations, a progression of the lesions noted in the 1-year exposure group (at the same dose of HDI) was also noted.

The dose response effects noted in this study are summarized below:

0.175 ppm: Reticulocytosis (less serious LOAEL). Eye irritation observed in males only, first year only (less serious LOAEL). No observed effects (NOAEL) on the following systems: cardiac, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, dermal, ocular (females only), body weight, immunologic/lymphoreticular, neurological, reproductive.

0.025 ppm: Nasal cavity hyperplasia/metaplasia, lung epithelialization, alveolar macrophage accumulation (less serious LOAEL). No observed effects in hematological parameters (NOAEL).

0.005 ppm: Nasal cavity epithelial hyperplasia (minimal LOAEL).

Dose end point used for MRL derivation:

[ ] NOAEL [X]LOAEL

Uncertainty factors used in MRL derivation:

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

The LOAEL Human Equivalent Dose ($LOAEL_{HEC}$) was calculated using Equation 4-16 from EPA (1994):

$$LOAEL_{HEC} = LOAEL \times RGDR_r$$

where $RGDR_r$ is the Regional Gas Dose Ratio for the region of interest. For HDI, the region of interest for this exposure route and duration for the rat is the nasal cavity. Again using EPA (1994) guidance and the dose-response relationships observed in rats outlined above, HDI effects would be classified as extrathoracic. HDI is also classified as a Category 1 gas (see pages 3–38 and 3–39 of EPA 1994), hence, Equation 4-18 of EPA (1994) was used to calculate the $RGDR_{ET}$.

$$LOAEL_{[HEC]} = LOAEL \times RGDR_{ET}$$

$$LOAEL_{[HEC]} = (0.005 \text{ ppm}) \times (V_E/SA_{ET})_A / (V_E/SA_{ET})_H$$

$$LOAEL_{[HEC]} = 0.005 \text{ ppm} \times ([0.24 \text{ m}^3/\text{day} / 11.6 \text{ cm}^2)] / [20 \text{ m}^3 / 177 \text{ cm}^2]$$

$$LOAEL_{[HEC]} = 0.005 \text{ ppm} \times 0.183$$

$$LOAEL_{[HEC]} = 0.0009 \text{ ppm}$$

Therefore:

$$MRL = LOAEL_{[HEC]} / UF$$

$$MRL = 0.0009 \text{ ppm} / 90$$

$$MRL = 1.0 \times 10^{-5} \text{ ppm}$$

where the $LOAEL_{[HEC]}$ is the Human Equivalent Concentration for the lowest-observed-adverse-effect level, the RGDR is the Regional Gas Dose Ratio (animal (A): human (H)), V_E is the ventilation volume (tidal volume in m^3/day), SA is the regional surface area of the toxic effect observed (in cm^2), and UF are the uncertainty factors.

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 only other study considered for deriving a chronic inhalation MRL was the epidemiological study by Alexandersson et al. (1987). Although the study showed promise as a human epidemiology study, these workers were exposed to the HDI monomer as well as to the HDI pre-polymers (biuret trimer). The study did not distinguish between the effects produced by the monomer versus the polymer; therefore, since this was a combination/mixture exposure, it was not considered appropriate for use in determining a chronic MRL. A study by Shepperly and Hathaway (1991) reported a NOAEL for workers exposed to HDI at concentrations of 5 ppb (0.005 ppm) or less at a plant in Freeport, Texas. A later study by

APPENDIX A

DeWilde and Hathaway (1994), again using chronically exposed workers at the plant in Freeport, Texas, found no statistically significant differences in pulmonary function data among HDI-exposed individuals and the control group. The dose in that study was estimated to be between 0.5 and 7 ppb (0.0005-0.007 ppm). Both the Shepperly and Hathaway (1991) and the DeWilde and Hathaway (1994) studies provided estimates of doses to which the workers were exposed, but could not provide definitive exposure doses to the worker populations. Both studies also had a number of difficulties (discussed above), which precluded their use in deriving a chronic-duration MRL based on human exposures, but they do lend some support to the MRL based on results found using the rat model.

It should be noted that the EPA Reference Concentration (RfC) for HDI was based on the same study as this chronic-duration inhalation MRL (Mobay 1989) and was also calculated to be $1.0x10^{-5}$ ppm. A report by Foureman et al. (1994) described how this RfC was derived using the 0.005 ppm as the NOAEL dose end point; for purposes of chronic-duration inhalation MRL derivation, the MRL was based on the same dose end point, but was classified as a minimal LOAEL. Fouremen et al. (1994) argue that although an effect was seen at the 0.005 ppm dose (nasal epithelial hyperplasia), this response should be classified as an adaptive response (as noted with many types of other irritants) and not a true toxic response, and therefore should be classified as a NOAEL. Fouremen et al. (1994) conclude that the olfactory degenerative response should be considered the significant effect in these rats, and not the hyperplastic response, supported by the fact that the degeneration of the olfactory epithelium did follow a concentration-response relationship for both incidence and severity. In contrast, the hyperplastic and inflammatory responses followed the traditional dose-response for incidence, but not for severity of the lesions. The ATSDR Minimal Risk Level Workgroup carefully reviewed this data and the arguments presented by the Fouremen et al. (1994) report and concluded that the degeneration of the olfactory epithelium was an adverse (toxic) response and warranted a classification as a minimal LOAEL. After uncertainty factors were applied, the RfC and the MRL concentration values resulted in the same value, $1.0x10^{-5}$ ppm, despite the differences in end point classification. This study involving the exposure of rats to HDI demonstrates that the line between an adaptive and toxic response in not always clearly defined, and it may be a matter of opinion as to whether the effects are true adverse toxic responses.

Agency Contact (Chemical Managed): Henry Abadin

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-l and Figure 2-l are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(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.

APPENDIX B

(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 "1 Sr" 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 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. 198 1.

(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 end point 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.

APPENDIX B

(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 end point 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 (qi*).

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

APPENDIX B

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).

SAMPLE

1 →

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

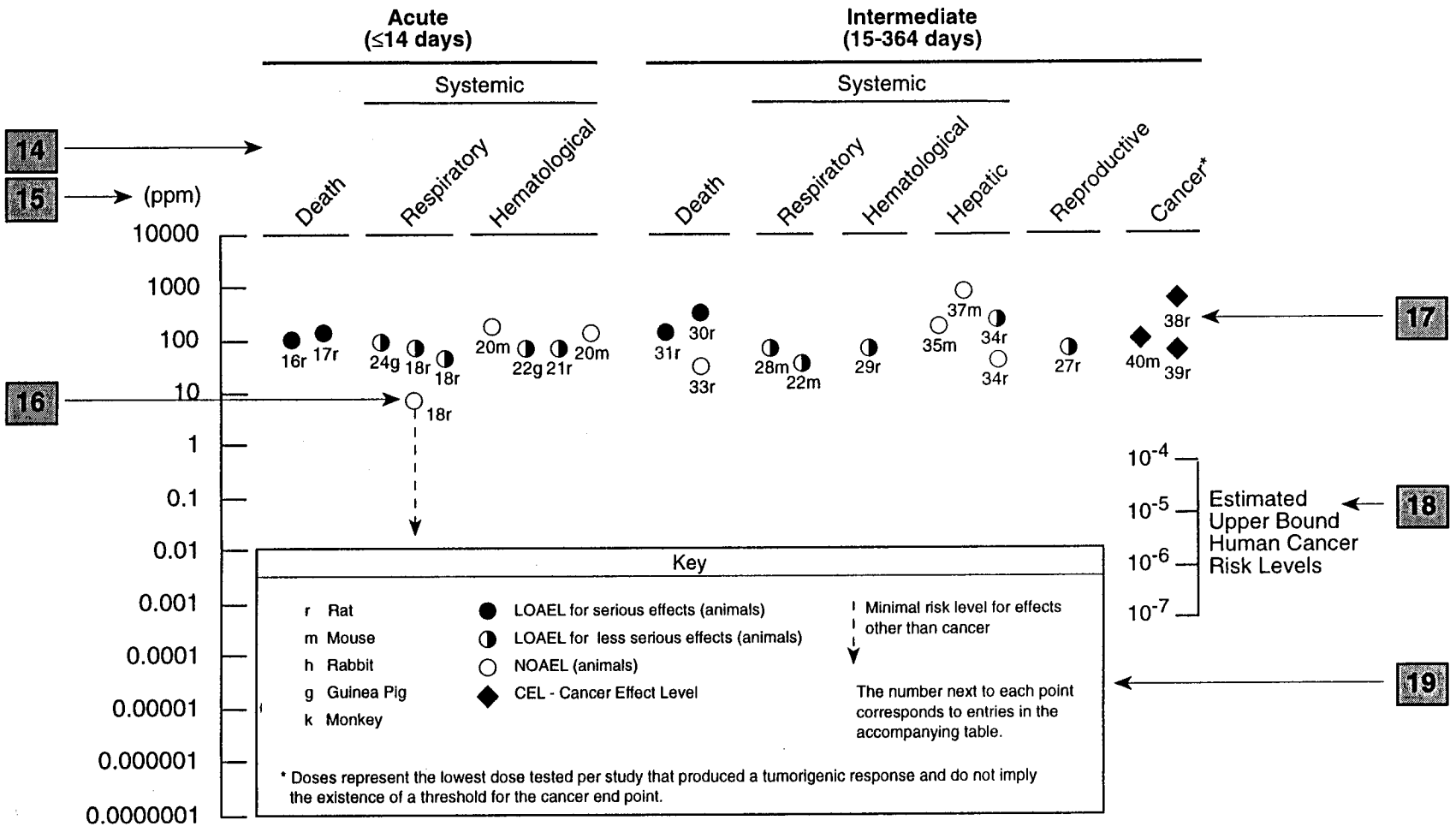
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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



APPENDIX B

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point 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-adverseeffect 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
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient

L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
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
OSHA	Occupational Safety and Health Administration
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