APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical Name:	Titanium tetrachloride
CAS Number:	7550-45-O
Date:	November 14, 1995
Profile Status:	Third Draft Post Public Comment
Route:	[X] Inhalation [ ] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Graph Key:	5r
Species:	Rat

Minimal Risk Level: 0.01 [X] mg/m^3 [ ] ppm

Reference: DuPont 1979

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Male Charles River (CD) rats (25/exposure concentration) were exposed to 0, 5, 10, or 40 mg/m^3 of atmospheric titanium tetrachloride allowed to hydrolyze in normal air for 6 hours/day, 5 days/week, for 4 weeks. Hematology, clinical chemistry, and urine tests, were conducted on 10 rats/group after the last exposure and after a 2-week recovery period. Five rats/group were necropsied on the last exposure day, after 2 weeks, and at 3, 6, and 12 months post-exposure. Blood and urine δ-aminolevulinic acid were determined at l-week intervals during the exposure period and 2 weeks post-exposure. All major organs and tissues were examined grossly and microscopically.

Effects noted in study and corresponding doses: Two rats in the high-exposure group died on test days 15 and 23. Death was attributed to respiratory failure triggered by partial obstruction of the tracheal lumen with precipitated dust particles, denuded tracheal epithelium, acute obliterative bronchiolitis, interstitial pneumonitis, pulmonary edema, and hemorrhage. In the high-exposure group, body weight gain was depressed by about 19% relative to controls by the end of the 4-week exposure period, but this trend was reversed during the recovery period. Treatment-related effects consisted of a decrease in δaminolevulinic acid dehydrase, a decrease in BUN and urine osmolality, and higher urinary pH in the mid- and high-exposure groups; these values returned to normal after a 2-week recovery period. Results from clinical chemistry and hematology tests revealed no significant deviations from normal ranges. Results from pathological examination showed that rats in the low-exposure group, sacrificed up to one year after exposure, had only a mild lung dust cell reaction. The mid- and high-exposure groups showed a concentration-dependent inflammation of the respiratory tract. Alterations consisted of acute bronchiolitis, interstitial pneumonitis, proliferation of alveolar cells, and hyperplasia of the tracheal epithelium with hypermucous secretion. These lesioins gradually disappeared after recovery and dust cells became sharply focalized. Collagenized fibrosis in the bronchioles and adjoining alveolar walls persisted throughout the 12-months recovery period. Relative lung weight was significantly elevated in all treated groups on the last exposure day and on the mid-and high-exposure groups 2 weeks post-exposure. Lung weight returned to normal 3 months post-exposure. There were no compound-related pathological lesions in the other organs and tissues examined.

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Dose and end point used for MRL derivation: The 5 mg/m^3 exposure concentration is considered a less serious LOAEL for mild dust cell reaction and increased relative lung weight.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans
[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: Rats were exposed in stainless steel chambers under dynamic air conditions. No information was provided regarding the method for generating the titanium tetrachloride atmospheric hydrolysis products. Because the rats were exposed to an aerosol and the critical effect was respiratory, Equation 4-5 in Interim Methods for Development of Inhalation Reference Concentrations (EPA 1990) was used to calculate the HEC (Human Equivalent Concentration). However, the only information provided regarding the size parameters of the aerosol particles was that the diameter ranged from 1 to 400 pm. Therefore, a default method was used to determine the ratio of the dose available for uptake from the thoracic region of the experimental animal species to that of humans ($RDDR_{TH}$). Examination of Table H-l in EPA (1990) revealed that the most conservative value of $RDDR_{TH}$ for any sigma g for the thoracic region is 0.2064. The $LOAEL_{HEC}$ was thus calculated as follows:

$$LOAEL_{HEC} = LOAEL \times RDDR_{TH}$$

$$= 5\ mg/m^3 \times 0.2064$$

$$= 1.032\ mg/m^3$$

where:

$LOAEL_{HEC}$ = Human Equivalent Concentration of the LOAEL (lowest-observed-adverse effect level)

$RDDR_{TH}$ = Regional Deposited Dose Ratio for Respiratory Effects in the Thoracic Region

Thus, the proposed intermediate inhalation MRL is derived as follows:

$$MRL = LOAEL_{HEC} \div UF$$

$$MRL = 1.032\ mg/m^3 \div 90$$

$$MRL = 0.01\ mg/m^3$$

Was a conversion used from intermittent to continuous exposure? No

Other additional studies or pertinent information that lend support to this MRL: Several studies in humans lend support to deriving a MRL. A health hazard evaluation of workers employed in a metal reduction factory suggests that exposure to titanium tetrachloride and its hydrolysis products may cause pulmonary impairment (Garabrant et al. 1987; Moseley et al. 1982). The data from those studies support the notion that chronic exposure to titanium tetrachloride may result in restrictive pulmonary changes. However, the concomitant exposure to other chemicals, such as titanium oxide, titanium dichloride, titanium oxychloride, sodium, sodium hydroxide, and sodium oxide prevents a more definitive determination of the role of titanium tetrachloride. Irritation of the upper and lower respiratory tract is observed in humans following acute inhalation exposure to titanium tetrachloride (Park et al. 1984; Ross 1985). The respiratory irritation may lead to cough, wheezing, dyspnea, respiratory distress, and hypoxia. In some cases, impairment of the respiratory function may continue for several weeks following exposure (Park et al. 1984).

Acute inhalation studies in animals lend support for a MRL derivation. Acute exposure of rats to 1,466, 5,122, 7,529 and 11,492 mg/m^3 of titanium tetrachloride resulted in wet noses, nasal discharge, dyspnea, and swollen eyelids (Karlsson et al. 1986). No deaths were found. Histopathology performed 7 days after exposure was essentially normal and revealed only minor lung lesions. The lungs in l/3 and 2/2 animals exposed to 5,122 and 11,492 mg/m^3, respectively, showed discrete inflammatory residues, coarsened alveolar septa, and sparse accumulation of phagocytes. Rats exposed to 1,200 mg/m^3 titanium tetrachloride for 30 minutes had severe inflammation of the respiratory epithelium 1 day post-exposure (DuPont 1980). Forty-nine days post-exposure the respiratory epithelium had normal appearance.

In a chronic study, Sprague-Dawley rats (l00/sex/exposure concentration) were exposed to 0, 0.1, 1.0, or 10.0 mg/m^3 of atmospheric titanium tetrachloride allowed to hydrolyze in normal air for 6 hours/day, 5 days/week, for 104 weeks. The most significant finding was the increased incidence of rhinitis and tracheitis with exposure concentration. In the low-exposure group the incidence of rhinitis was also duration-dependent and ranged from 4.3 to 15% after 1 year of treatment, and from 22 to 64% at the end of the second year. Similar observations were made in the mid- and high-exposure groups. Tracheitis also increased with exposure duration, and to a lesser degree with concentration. The two highest groups had increased incidence of tracheitis as early as 3 months, and at the end of 2 years was also increased in the lowest exposure group. The incidences of tracheitis at the end of the 2 years were O-2.5%, 12-20%, 41-49%, and 30-44% for the control, low-, mid-, and high-exposure groups, respectively. Gross pathology and histopathology revealed compound-related changes in the lungs and thoracic lymph nodes of the treated animals.
Agency Contact (Chemical Manager): Ed Murray

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MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Titanium tetrachloride
CAS Number: 7550-45-0
Date: November 14, 1995
Profile Status: Third Draft Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 6r
Species: Rat

Minimal Risk Level: 0.0001 [X] mg/m^3 [ ] ppm

Reference: EPA 1986; Lee et al. 1986

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Charles River (CD) rats (l00/sex/exposure concentration) were exposed to 0, 0.1, 1.0, or 10.0 mg/m^3 atmospherically hydrolyzed titanium tetrachloride for 6 hours/day, 5 days/week, for 104 weeks. Five males and 5 females from each group were sacrificed after 3 and 6 months, 10 animals of each sex were killed after 1 year, and the remaining animals were sacrificed at the end of the second year for gross and microscopic evaluation.

Effects noted in study and corresponding doses: The major health effects of exposure were observed in the respiratory tract of the exposed animals. The primary observation was an increased incidence of irregular breathing and lung noises in the exposed rats that was concentration-dependent. This respiratory effect was present in males (8, 12, 24, and 36%) and females (8, 16, 44, and 41%) exposed to 0, 0.1, 1 .O and 10 mg/m^3, respectively. The incidence of rhinitis and tracheitis also increased with concentration. In the low-exposure group the incidence of rhinitis was also duration-dependent and ranged from 4.3 to 15% after 1 year of treatment, and from 22 to 64% at the end of the second year. Similar observations were made in the mid- and high-exposure groups. Tracheitis also increased with exposure duration, and to a lesser degree with concentration. The 2 highest groups had increased incidence of tracheitis as early as 3 months, and at the end of 2 years was also increased in the lowest exposure group. The incidences of tracheitis at the end of the 2 years were O-2.5%, 12-20%, 41-49%, 30-44% for the control, low-, mid-, and high-exposure groups, respectively. The 0.1 mg/m^3 is considered a less serious LOAEL for adverse effects in the tracheobronchial region. Gross pathology and histopathology revealed compound-related changes in the lungs and thoracic lymph nodes of the treated animals. Foci laden with yellow titanium tetrachloride hydrolysis products were present on the lung pleural surface and on the slightly enlarged tracheobronchial lymph nodes in the mid- and highexposure groups. The pulmonary response in these two groups also included the presence of the dustladen macrophages, and the hyperplasia of the alveolar lining. The incidence and severity of alveolar hyperplasia increased with concentration; it was 0% in the control and low-exposure groups, and 32-63% and 92-97% in the mid- and high-exposure groups.

Dose and end point used for MRL derivation: The 0.1 mg/m^3 is considered a less serious LOAEL for increased incidence of rhinitis and tracheitis.

[ ] NOAEL [X] LOAEL

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Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans
[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: Rats were exposed in stainless steel chambers under dynamic air conditions. Vapors of titanium tetrachloride were generated by passing nitrogen over liquid titanium tetrachloride. Chamber atmospheres were monitored by trapping the solid titanium tetrachloride hydrolysis products on cellulose acetate filters which were analyzed for titanium content. The mass median diameter of the aerosol particles was about 0.5 μm with a geometric standard deviation of about 2 μm. Because the rats were exposed to an aerosol and the critical effect was respiratory, Equation 4-5 in Interim Methods for Development of Inhalation Reference Concentrations (EPA 1990) was used to calculate the HEC (Human Equivalent Concentration). Table H-l in EPA (1990) was used to determine the ratio of the dose available for uptake from the extrathoracic region of the respiratory system of the experimental animal species to that of humans ($RDDR_{ET}$). The RDDR for the ET region corresponding to a mass median aerodynamic diameter (MMDA) of 0.5 μm with a Sigma g of 2.0 μm is 0.1201. The $LOAEL_{HEC}$ was calculated as follows:

$$LOAEL_{HEC} = LOAEL \times RDDR_{ET}$$

$$= 0.1 \times 0.1201$$

$$= 0.01201 \text{ mg/m}^3$$

where:

$LOAEL_{HEC}$ = Human Equivalent concentration of the LOAEL (lowest-observed-adverse effect level)

$RDDR_{ET}$ = Regional Deposited Dose Ratio for Respiratory Effect in the Extrathoracic Region

Thus, the proposed chronic inhalation MRL was derived as follows:

$$MRL = LOAEL_{HEC} \div UF$$

$$MRL = 0.01201 \text{ mg/m}^3 \div 90$$

$$MRL = 0.0001 \text{ mg/m}^3$$

Was a conversion used from intermittent to continuous exposure? The LOAEL was not adjusted for intermittent exposure because the effects reflect contact irritation.

Other additional studies or pertinent information that lend support to this MRL: Several studies in humans lend support to deriving a MRL. A health hazard evaluation of workers employed in a metal reduction factory suggests that exposure to titanium tetrachloride and its hydrolysis products may cause pulmonary impairment (Garabrant et al. 1987; Moseley et al. 1982). The data from those

studies support the notion that chronic exposure to titanium tetrachloride may result in restrictive pulmonary changes. However, the concomitant exposure to other chemicals, such as titanium oxide, titanium dichloride, titanium oxychloride, sodium, sodium hydroxide, and sodium oxide prevents a more definitive determination of the role of titanium tetrachloride. Irritation of the upper and lower respiratory tract is observed in humans following acute inhalation exposure to titanium tetrachloride (Park et al. 1984; Ross 1985). The respiratory irritation may lead to cough, wheezing, dyspnea, respiratory distress, and hypoxia. In some cases, impairment of the respiratory function may continue for several weeks following exposure (Park et al. 1984).

Acute inhalation studies in animals also lend support for the MRL derivation. Acute exposure of rats to 1,466, 5,122, 7,529, and 11,492 mg/m^3 of titanium tetrachloride resulted in wet noses, nasal discharge, dyspnea, and swollen eyelids. (Karlsson et al. 1986). No deaths were found. Histopathology performed 7 days after exposure was essentially normal and revealed only minor lung lesions. The lungs in l/3 and 2/2 animals exposed to 5,122 and 11,492 mg/m^3, respectively, showed discrete inflammatory residues, coarsened alveolar septa, and sparse accumulation of phagocytes. Rats exposed to 1,200 mg/m^3 titanium tetrachloride for 30 minutes had severe inflammation of the respiratory epithelium 1 day post-exposure (DuPont 1980). Forty-nine days post-exposure the respiratory epithelium had normal appearance. Rats exposed to 5 mg/m^3 6 hours/day, 5 days/week for 4 weeks a mild lung dust cell reaction and increased relative lung weight; both effects were reversible (DuPont 1979). Exposure to $\geq$10 mg/m^3, however, induced bronchiolitis, interstitial pneumonitis, alveolar cell proliferation, hyperplasia of the tracheal epithelium, and collagenized fibrosis. These effects gradually disappeared over a 12-month recovery period. No studies were located regarding reproductive or developmental effects in humans or animals after exposure to titanium tetrachloride by any route.

Agency Contact (Chemical Manager): Ed Murray

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

LEGEND

See LSE Table 2-1

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

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

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

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

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

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

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

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

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

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

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

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

LEGEND

See Figure 2-1

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

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

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

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

(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_l*).

(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

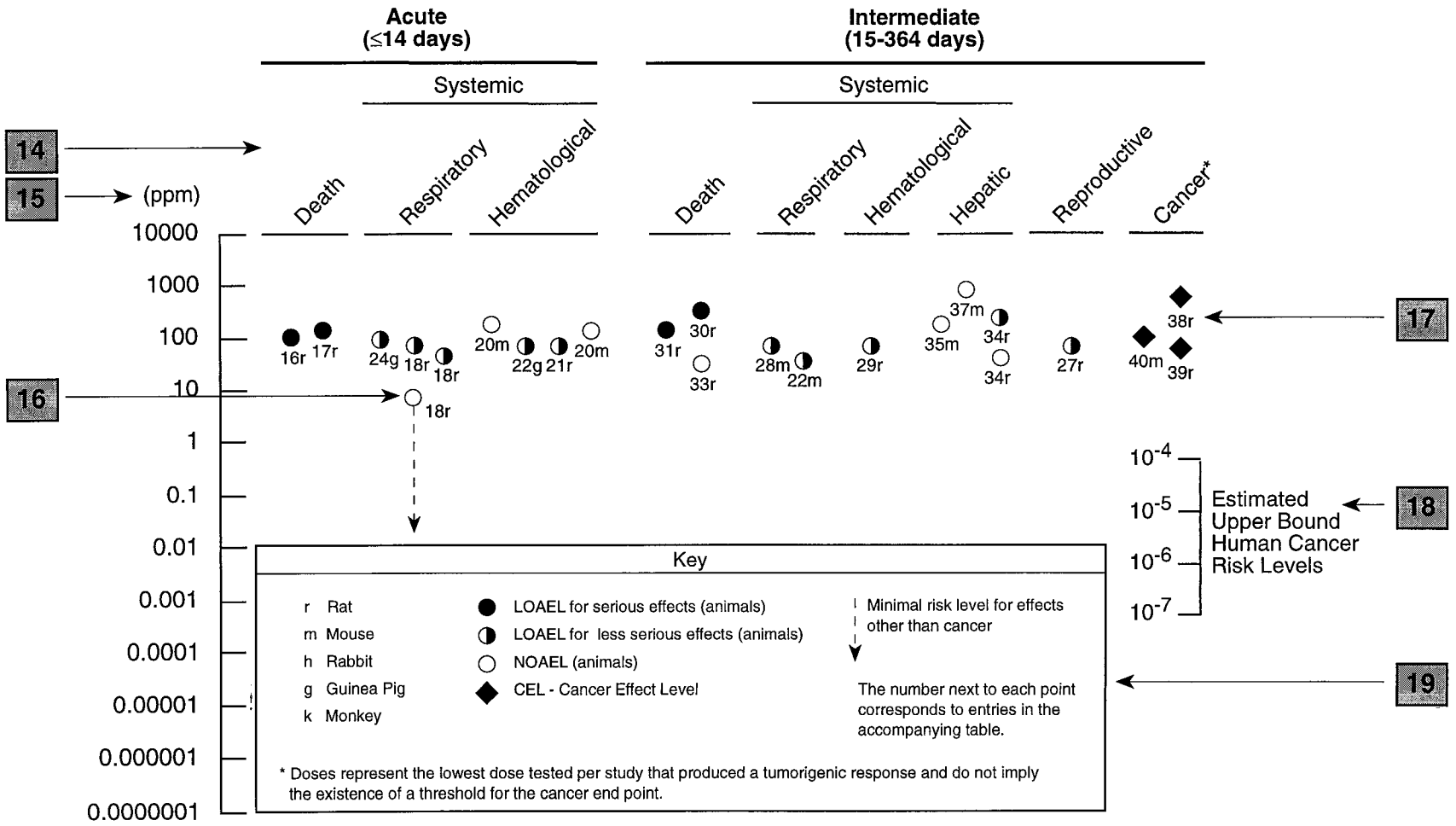
[a] The number corresponds to entries in Figure 2-1.

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

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

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



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).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observedadverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
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

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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
mm Hg	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

APPENDIX C

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