TOXICOLOGICAL PROFILE FOR
TITANIUM TETRACHLORIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Titanium Tetrachloride was released on June 1994. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

</div>

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Super-fund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Edward Murray, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Fernando Llados, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1 .   Green Border Review. Green Border review assures consistency with ATSDR policy.

2 .   Health Effects Review. The Health Effects Review Committee examines the health effects
        chapter of each profile for consistency and accuracy in interpreting health effects and
        classifying end points.

3 .   Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to
        substance-specific minimal risk levels (MRLs), reviews the health effects database of each
        profile, and makes recommendations for derivation of MRLs.

4 .   Quality Assurance Review. The Quality Assurance Branch assures that consistency across
        profiles is maintained, identifies any significant problems in format or content, and establishes
        that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for titanium tetrachloride. The panel consisted of the following members:

1 . Dr. Hugh Farber, Private Consultant, Lake Leelanau, MI;

2 . Dr. Arthur Gregory, Private Consultant, Sterling, VA; and

3 . Mr. Lyman Skory, Skory Consulting, Midland, MI.

These experts collectively have knowledge of titanium tetrachloride's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about titanium tetrachloride and to emphasize the human health effects that may result from exposure to it.

The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Titanium tetrachloride has not been found in any of the sites on the NPL. However, the number of NPL sites evaluated for titanium tetrachloride is not known. As EPA evaluates more sites, the number of sites at which titanium tetrachloride is found may change. This information is important because exposure to titanium tetrachloride may cause harmful health effects. However, since titanium tetrachloride breaks down rapidly in the environment, it is unlikely that you would be exposed to it at disposal sites.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as titanium tetrachloride, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS TITANIUM TETRACHLORIDE?

Titanium tetrachloride is a colorless to pale yellow liquid that has fumes with a strong odor. If it comes in contact with water, it rapidly forms hydrochloric acid, as well as titanium compounds. In 1990, approximately 1.5 million tons of titanium tetrachloride were produced in the United States.

Titanium tetrachloride is not found naturally in the environment and is made from minerals that contain titanium. It is used to make titanium metal and other titanium-containing compounds, such as titanium dioxide, which is used as a white pigment in paints and other products, and as an intermediary to produce other chemicals.

Chapter 3 contains more information on the physical and chemical properties of titanium tetrachloride, and Chapter 4 contains more information on its production and use.

1.2 WHAT HAPPENS TO TITANIUM TETRACHLORIDE WHEN IT ENTERS THE ENVIRONMENT?

Titanium tetrachloride enters the environment primarily as air emissions from facilities that make or use it in various chemical processes or as a result of spills. If moisture is present in the air, titanium tetrachloride reacts with the moisture to form hydrochloric acid and other titanium compounds, such as titanium hydroxide and titanium oxychlorides. The end-products produced when titanium tetrachloride reacts with water are titanium dioxide and hydrochloric acid. The hydrochloric acid may break down or be carried in the air. Some of the titanium compounds may settle out to soil or water. In water, they sink into the bottom sediments. They may remain. for a long time in the soil or sediments. Some other titanium compounds, such as titanium dioxide, are also found in the air and water. See Chapters 4 and 5 for more information on what happens to titanium tetrachloride in the environment.

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1.3   HOW MIGHT I BE EXPOSED TO TITANIUM TETRACHLORIDE?

Titanium tetrachloride has not been found in water, soil, food, or air except in the workplace. Because titanium tetrachloride breaks down so rapidly in the environment, you would probably not be exposed to it unless you worked in a facility that made or used it, or you were exposed to it as a result of a spill. If you work at such a facility, you may breathe in air that contains it or breathe fumes of hydrochloric acid. You could also breathe in particles of titanium dioxide or titanium metal dust. If titanium tetrachloride spills, you may get it on your skin. In 1980, about 2,100 workers may have been exposed to titanium tetrachloride in the workplace. Since titanium tetrachloride breaks down rapidly in the environment, it is unlikely that you would be exposed to it at disposal sites.

No other information has been found on the presence of titanium tetrachloride in air, water, soil, or foods that would suggest that you may be exposed to it from these sources. See Chapter 5 for more information on the potential for exposure to titanium tetrachloride.

1.4   HOW CAN TITANIUM TETRACHLORIDE ENTER AND LEAVE MY BODY?

The fumes from titanium tetrachloride can easily enter your body if you breathe air that is contaminated with it. In your nose and lungs, these fumes may cause burns. Particles that contain titanium may remain in your lungs or nearby tissue. Titanium tetrachloride and its breakdown products do not appear to enter other parts of your body. See Chapter 2 for more information on how titanium tetrachloride may enter and leave your body.

1.5   HOW CAN TITANIUM TETRACHLORIDE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.
One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal

1. PUBLIC HEALTH STATEMENT

testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Titanium tetrachloride can be very irritating to the skin, eyes, mucous membranes, and the lungs. Titanium tetrachloride is corrosive because it reacts strongly with water to produce hydrochloric acid. The reaction products, especially hydrochloric acid, cause the harmful health effects and burns that can occur after exposure to titanium tetrachloride. Breathing in large amounts of titanium tetrachloride can injure the lungs seriously enough to cause death. We do not know how much of the compound is necessary to cause death. After short-term exposure to titanium tetrachloride, less serious respiratory system effects can include coughing and tightness in the chest. More severe effects can include chemical bronchitis or pneumonia, and congestion of the mucous membranes of the upper respiratory tract. These effects can cause long-term effects such as the narrowing of the vocal cords, windpipe, and upper airways. Although there are no data on swallowing titanium tetrachloride, it is likely that eating large amounts of this chemical could also cause death.

Accidental exposure to liquid titanium tetrachloride can result in skin burns and can cause permanent damage to the eyes if they are not protected.

Some laboratory animals that breathed titanium tetrachloride fumes for 2 years developed lung tumors of a special type. However, there is no evidence that chronic exposure to titanium tetrachloride causes cancer in humans. There is not enough information to determine if titanium tetrachloride causes birth defects or affects reproduction. Titanium tetrachloride has not been classified for its carcinogenic properties. For more information on the health effects of titanium tetrachloride, see Chapter 2.

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1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TITANIUM TETRACHLORIDE?

There is no medical test to indicate whether you have been exposed to titanium tetrachloride. However, you can be tested for the presence of titanium dioxide or titanium metal, which are breakdown products of titanium tetrachloride. This test uses electron microscopes to examine lung tissue for particles that contain titanium. This test is not specific for titanium tetrachloride exposure, but it does indicate exposure to some titanium-containing substances.

Also, the test does not indicate whether you may have potential health effects resulting from such exposure or the amount of titanium compound to which you were exposed. See Chapters 2 and 6 for more information on determining exposure to titanium tetrachloride.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations m be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals, then they are adjusted to help protect people: Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an S-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for titanium tetrachloride include the following:

- Releases of more than 1 pound of titanium tetrachloride must be reported to EPA.
- Maximum levels have not been established for titanium tetrachloride exposure in the workplace.

See Chapter 7 for more information on the regulations and guidelines that have been established for titanium tetrachloride.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333
(404) 639-6000

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of titanium tetrachloride. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect---death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

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at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for titanium tetrachloride. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are' acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

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2.2.1 Inhalation Exposure

Titanium tetrachloride is a colorless-to-light-yellow liquid with a penetrating acid odor (Merck 1989). Titanium tetrachloride can be highly irritating to the mucous membranes (including the upper respiratory tract), the skin, and the eyes (Mogilevskaja 1983). It is a highly corrosive acute irritant to the skin, eyes, mucous membranes, and respiratory tract (EPA 1985b). Titanium tetrachloride readily hydrolyzes in the presence of water or moist air via an exothermic reaction that occurs in two stages. First, titanium tetrachloride reacts to form a highly dispersed particulate smoke. This smoke reacts with more moisture in the air to form hydrolytic products of titanium tetrachloride such as hydrochloric acid, titanium oxychlorides, and titanium dioxide. Titanium tetrachloride is used as an intermediate in the production of metallic titanium and titanium dioxide. It is reduced in the presence of metallic sodium to yield a solid mixture of titanium and sodium chloride (Garabrant et al. 1987). Titanium tetrachloride can also be used for the generation of white smoke screens in military operations (Wilms et al. 1992), in the pigment and mordant dye industry, and in glass and pearl manufacturing (EPA 1985b). Because of its rapid evaporation and smoke formation, exposure to titanium tetrachloride is most likely to occur via the inhalation route. The highly corrosive properties of titanium tetrachloride that have been described in accidental occupational exposure studies are probably due to its rapid hydrolysis by water to yield hydrochloric acid (EPA 1985b).

All of the human studies discussed in the section on inhalation exposure are either epidemiological reports of occupational exposure or case reports of accidental exposure. In most occupational studies and in reports of accidental exposure, the exact levels of exposure are not known. It should be also noted that in occupational exposure settings, dermal exposure may occur simultaneously with inhalation exposure.

Many inhalation studies in animals were conducted with titanium tetrachloride passing through or into a chamber containing moist air which causes hydrolysis to occur. The extent of hydrolysis will depend on the amount of water and the residence time before inhalation occurs. Thus, it. is hard to determine exactly the composition of the mixture (unhydrolyzed titanium tetrachloride plus hydrolysis products) that the animal breathed.

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2.2.1.1 Death

One death was reported in the case of a worker who was accidentally splashed his whole body with titanium tetrachloride (Chitkara and McNeela 1992). He suffered extensive burns to his facial skin, nasopharynx, and larynx, and both his eyes were severely injured. His corneas were thick and opaque with extensive swelling of the bulbar conjunctiva and episclera. Over the next 14 days, some of the opacity in the right eye cleared, but there was no improvement in the left eye. The patient died from the complications of severe pulmonary injury caused by inhalation of titanium tetrachloride fumes (Chitkara and McNeela 1992).

Except for the single case described above, no increase in mortality from any cause was reported in workers occupationally exposed to titanium tetrachloride from one day to over five years (EPA 1990b; Fayerweather et al. 1992). However, these studies are limited because they are focused to some extent on the incidence of, and mortality from, lung cancer and because of the confounding effect of potential exposure of the subjects to other chemicals in the chemical manufacturing complex. Exposure to other chemicals confounds matching of the controls and the exposed individuals.

Limited information was located regarding lethal effects in animals after inhalation exposure to titanium tetrachloride. The 4-hour and 2minute inhalation LC_{50} values in rats exposed head-only were 460 mg/m^3 and 108,000 mg/m^3, respectively (DuPont 1980); other LC_{50} values fall in between. Death was attributed to pulmonary edema and occurred during exposures and up to one week post exposure. After or during a single 2-hour inhalation exposure to various levels of titanium tetrachloride and its hydrolysis products (titanium oxychloride, titanium dioxide and hydrochloric acid), 9 of 15 mice died (Mezentseva et al. 1963). The results indicate that death following exposure was concentration-dependent; of the 9 animals that died following exposure to titanium tetrachloride, 4 were from the high-dose group, 3 were from the middle-dose group, and 2 were from the low-dose group. This study also included 3 groups of mice exposed to hydrochloric acid alone (the concentrations were 0.012-0.06 mg/L, 0.036-0.11 mg/L, and 0.03-0.24 mg/L). Only one mouse died in the group exposed to the high dose of hydrochloric acid. These results are important because they compare the toxic effects of titanium tetrachloride and its hydrolysis products with those of hydrochloric acid, and they suggest that titanium tetrachloride and subsequent hydrolysis products are more toxic to mice than hydrochloric acid alone. Although the cause of death in this study is not known, it appeared that in both cases (exposure to hydrolysis products of titanium tetrachloride and

exposure to hydrochloric acid alone) the ultimate toxicant was hydrochloric acid. One possible explanation for the more severe effects seen from exposure to titanium tetrachloride compared with hydrochloric acid is that hydrochloric acid, because of its high solubility, is dissolved in the moisture of the nasopharynx and trachea and thus penetrates the lungs to only a very limited extent. However, in the case of exposure to titanium tetrachloride, the hydrolysis occurs in several steps; one of the hydrolysis products, titanium oxide hydrate, is a particulate that can absorb some of the hydrochloric acid vapors that are also generated during hydrolysis and carry them into the deeper parts of the lungs. Also, in the lungs, the partially hydrolyzed titanium tetrachloride can be further hydrolyzed with release of hydrochloric acid, resulting ultimately in hydrochloric acid being carried deeper into the lung and to the alveoli (Mezentseva et al. 1963). This study is limited in that the precise exposure levels are not known since the titanium tetrachloride concentrations were communicated as separate titanium concentrations and hydrochloric acid concentrations. The study also did not give detailed information on the exposed animals.

In a 4-week inhalation study, male rats were exposed to 0, 5, 10, or 40 mg/m^3 titanium tetrachloride 6 hours per day, 5 days per week (DuPont 1979). Two animals in the high-exposure group died on test days 15 and 23; the cause of death appeared to have been respiratory failure. Necropsy of these rats revealed partial obstruction of the tracheal lumen with precipitated dust particles, denuded tracheal epithelium, acute obliterative bronchiolitis, interstitial pneumonitis, pulmonary edema, and hemorrhage.

LOAEL values for death for each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to titanium tetrachloride. The systemic effects observed after inhalation exposure are discussed below.

The NOAEL and LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-l and plotted Figure 2-l.

TABLE 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
ACUTE EXPOSURE							
Death							
1	Rat (CD)	4 hr				460 M (4 hr LC$_{50}$)	DuPont 1980
Systemic							
2	Rat (CD)	30 min	Resp			1200 M (severe respiratory inflammation; epithelial denudation).	DuPont 1980
3	Rat (Sprague-Dawley)	10 min	Resp		1466 F (nasal discharge, dyspnea)	5112 F (discrete inflammatory residue in the lungs, coarsened alveolar septa)	Karlsson et al. 1986
			Ocular		1466 F (swollen eyelids)		
INTERMEDIATE EXPOSURE							
Death							
4	Rat (CD)	4 wk 5 d/wk 6 hr/d				40 M (2/25 deaths on test days 15 and 23)	DuPont 1979

TABLE 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL		Reference
					Less serious (mg/m3)	Serious (mg/m3)	
Systemic							
5	Rat (CD)	4 wk 5 d/wk 6 hr/d	Resp		5[b] M (reversible increase in relative lung weight; mild lung dust cell reaction)	10 M (brochiolitis, pneumonitis, alveolar cell proliferation, hyperplasia of tracheal epithelium, collagenized fibrosis)	DuPont 1979
			Cardio	40 M			
			Gastro	40 M			
			Hemato	40 M			
			Hepatic	40 M			
			Renal	5 M	10 M (increased urine pH and decreased osmolality)		
			Endocr	40 M			
			Dermal	40 M			
			Ocular	40 M			
			Bd Wt		40 M (19% reduction in body weight gain)		
CHRONIC EXPOSURE							
Systemic							
6	Rat (Crl:CD)	2 yr 5 d/wk 6 hr/d	Resp		0.1[c] (increased incidence of tracheitis and rhinitis)		EPA 1986; Lee et al. 1986
			Bd Wt	10			

TABLE 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)

Key to figure [a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m³)	LOAEL		Reference
					Less serious (mg/m³)	Serious (mg/m³)	
Immunological/Lymphoreticular							
7	Rat (CD)	2 yr 5 d/wk 6 hr/d		0.1	1.0 (increased incidence of foamy lung macrophages with increased TiCl₄ dust deposition)		EPA 1986; Lee et al. 1986

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

[b] Used to derive an intermediate inhalation Minimum Risk Level (MRL) of 0.01 mg/m³; LOAEL$_{HEC}$ divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

[c] Used to derive a chronic inhalation MRL of 0.0001 mg/m³; LOAEL$_{HEC}$ divided by an uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; Gastro = gastrointestinal; HEC = human equivalent concentration; Hemato = hematological; hr = hour(s); LC₅₀ = lethal concentration, 50% kill; LOAEL = lowest- observable-adverse-effect level; M = male; min = minutes; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation

Acute (≤ 14 days)
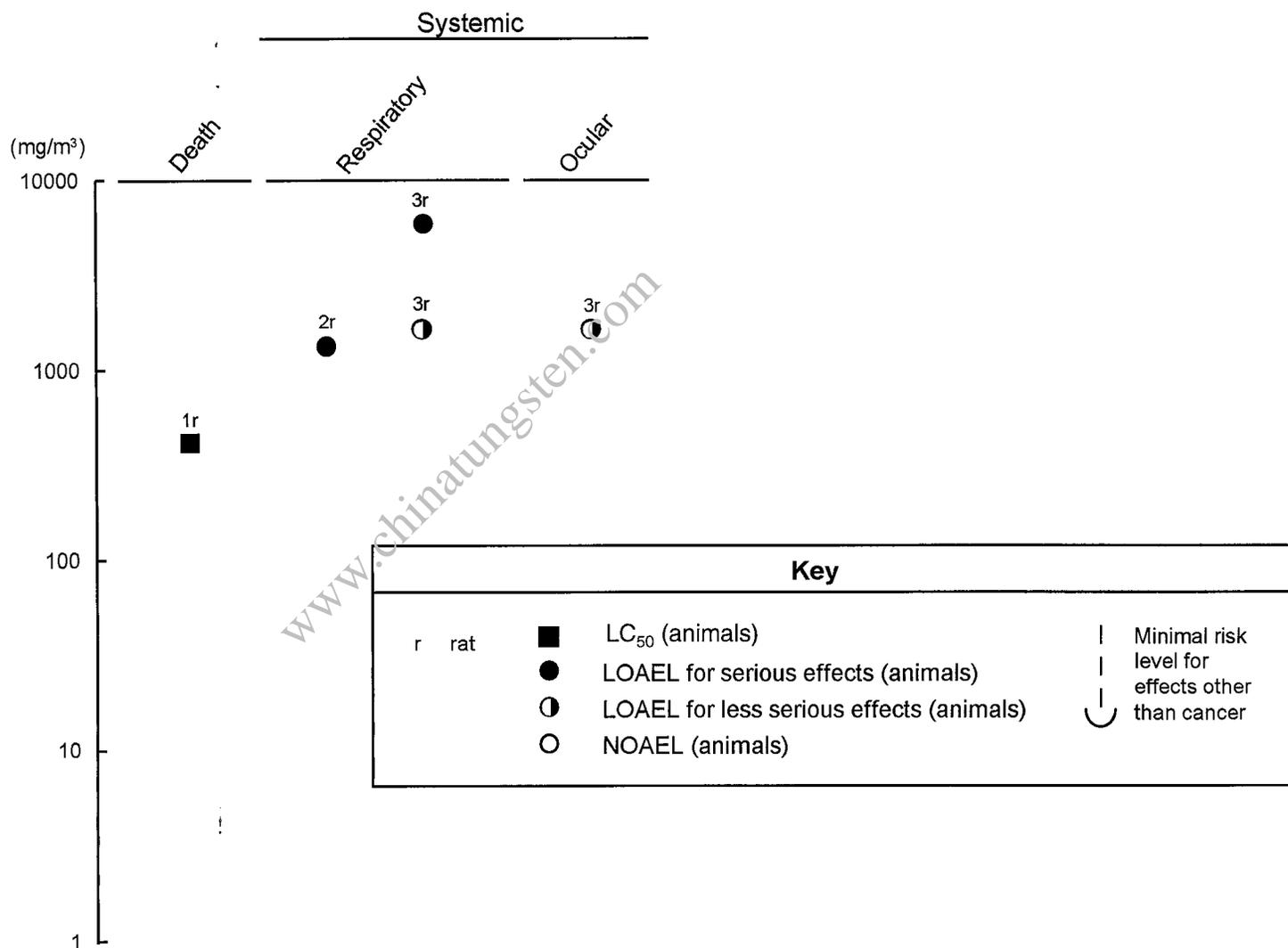
Figure 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)

Intermediate (15-364 days)
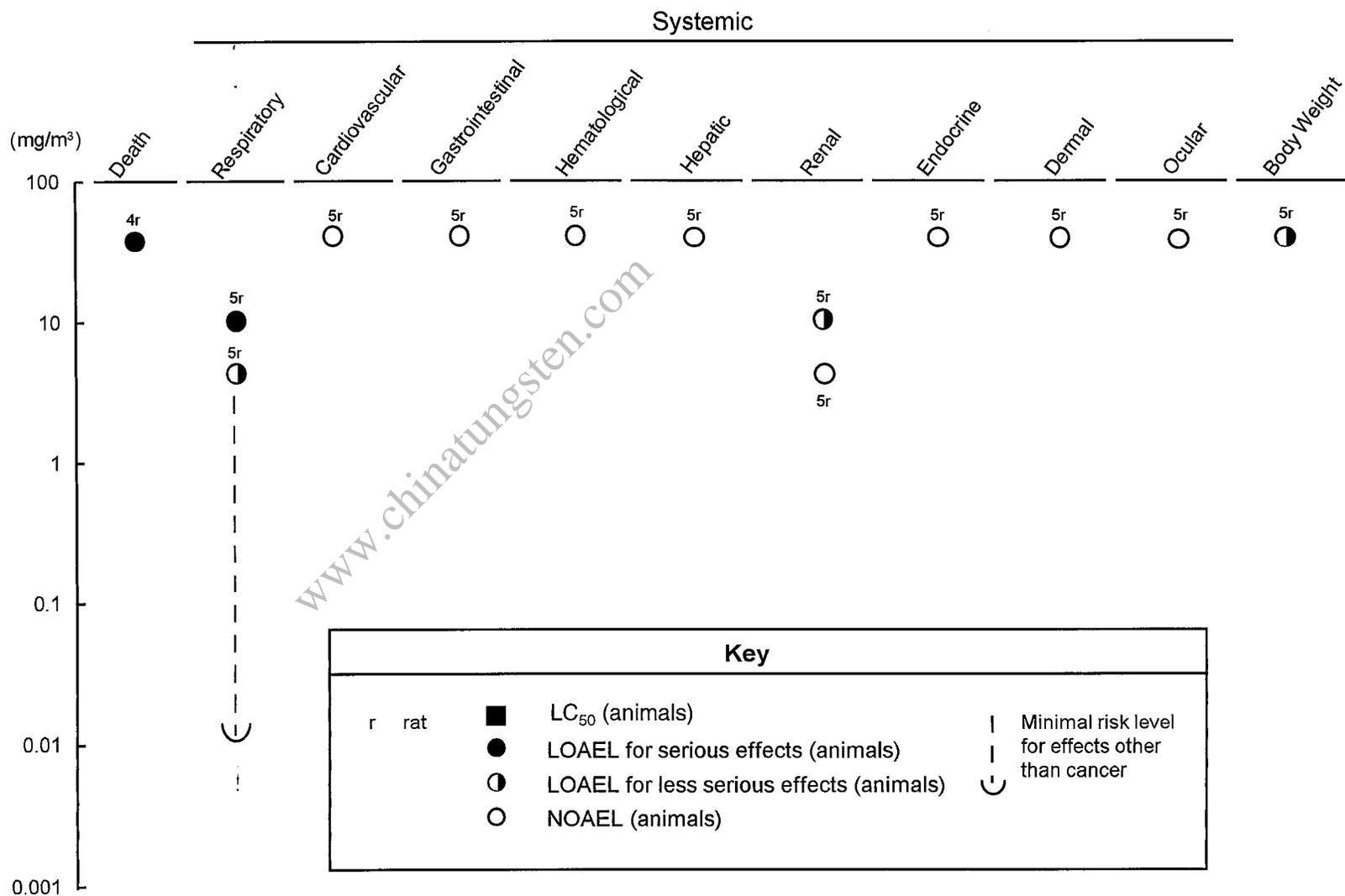
# Figure 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)

Chronic (≥ 365 days)

Key

r	rat	■	LC$_{50}$ (animals)
		●	LOAEL for serious effects (animals)
		◑	LOAEL for less serious effects (animals)
		○	NOAEL (animals)

Minimal risk level for effects other than cancer
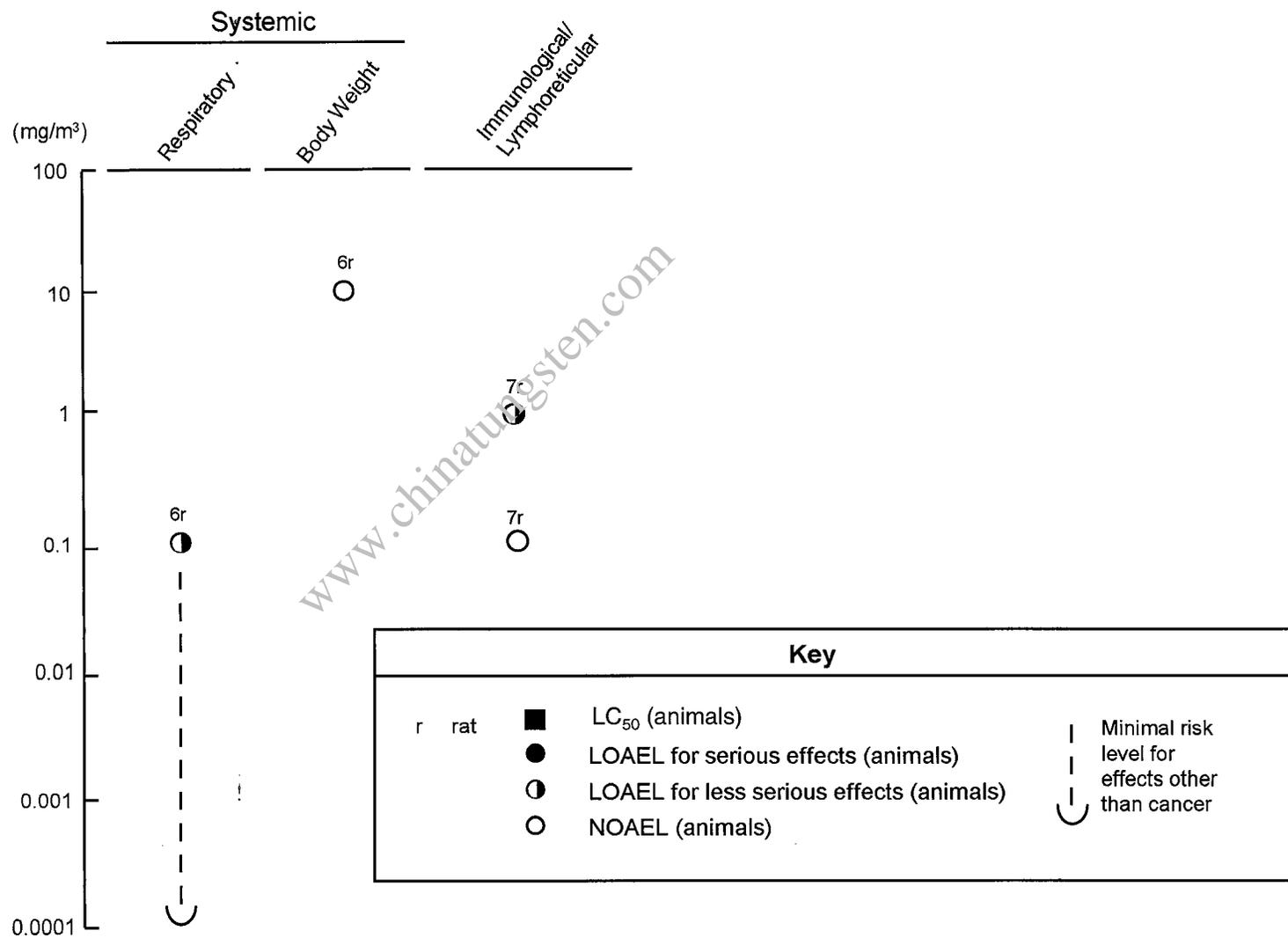
2. HEALTH EFFECTS

Respiratory Effects. Case studies of humans acutely exposed to titanium tetrachloride fumes have shown the irritant nature of the inhaled chemical. Since titanium tetrachloride undergoes hydrolysis almost immediately when in contact with water or moisture in the air (forming fumes that contain titanium oxychloride and hydrochloric acid), its main effect on the lungs is corrosive. Although the degree of pulmonary injury can vary, exposure can result in an intense chemical bronchitis or pneumonia (Lawson 1961). Following an accidental acute exposure, three research workers experienced only mild irritant symptoms consisting of cough and tightness in the chest, which both lasted only a couple of hours and left no abnormalities on the chest X-ray (Ross 1985). More severe pulmonary effects were reported in two other incidents of accidental exposure to titanium tetrachloride. One worker who was splashed with hot titanium tetrachloride suffered marked congestion of the mucous membranes of the pharynx, vocal cords, and trachea (Ross 1985). This exposure had long-term effects that included stenosis of the larynx, trachea, and upper bronchi. The second worker accidentally exposed to titanium tetrachloride hydrolysis fumes developed cough and dyspnea 20 minutes after exposure (Park et al. 1984). His symptoms progressed to severe upper airway distress that required intubation and ventilation. Further symptoms included hypoxia and diffuse pulmonary infiltrates suggestive of adult respiratory distress syndrome. He gradually improved, but fiberoptic bronchoscopy 5 weeks after admission revealed erythema of the entire bronchial tree and the presence of 35-40 fleshy polypoid lesions. The presence of the polyps, according to the authors, was a sign of an exaggerated but normal reparative process of the tracheobronchial injury. This delayed complication has been seen in thermal respiratory injuries, indicating that the severe adverse respiratory effects seen in this case may, in part, be due to the exothermic nature of the titanium tetrachloride hydrolysis reaction. One year after the injury, his lungs appeared normal, but some degree of mild stenosis remained.

The results of occupational exposure of 209 workers employed at a metals reduction facility in Ashtabula, Ohio, were reported in two retrospective studies (Garabrant et al. 1987; NIOSH 1980). The results suggest that pulmonary impairment may be caused by exposure to titanium tetrachloride. Medical examinations, chest X-rays, and pulmonary function tests were done on all workers. Medical and occupational histories were also obtained. Personal and area air samples were analyzed for titanium particulates, asbestos, welding fumes, and hydrochloric acid. NIOSH determined that the hydrochloric acid concentration in the air was negligible (below the OSHA standard of 5 mg/m^3). Workers were divided into three groups (two experimental and one control) based on their jobs and duration of employment in specific jobs. The use of a group of maintenance workers as a control may

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have caused the underestimation of the true association between respiratory symptoms and pleural disease because the controls had longer smoking histories and asbestos exposure. Of the 209 workers, 78 were engaged in the titanium tetrachloride reduction process and were also exposed to sodium, titanium dioxide particulates, and titanium oxychloride. There were no significant differences regarding symptoms, results of functional tests, and results of chest radiographs among the three groups. The symptoms utilized for comparison in this study were cough, phlegm production, chronic bronchitis, and wheezing with dyspnea. Logistic regression analysis of the chest radiograph data showed that pleural thickening was strongly related to the length of time spent working in titanium production (p< 0.001). The initial estimate of loss of pulmonary function, taking smoking into account, was 45 ml/year leading to a deficit of 1.8 L/40-year employment period (NIOSH 1980). Further analysis of the employees, based on job and duration of employment, confirmed large decreases in forced vital capacity (FVC) in workers employed in titanium tetrachloride reduction for at least 10 years (Garabrant et al. 1987). A regression analysis of the data adjusted for age, height, and smoking revealed that the rate of loss of FVC was 24 mL per year for the titanium tetrachloride workers (Garabrant et al. 1987). The results also showed that previous asbestos exposure and cigarette smoking were not significantly related to pleural thickening. These results suggest that chronic exposure to titanium tetrachloride may result in restrictive pulmonary changes and that there is no clear association between pleural thickening and reduction in ventilator-y capacity. It was difficult to determine the precise cause of these pulmonary abnormalities, and further studies are needed to clarify this issue. The limitations of both studies include the lack of information on the duration, route, and exposure levels, the concomitant exposure to a mixture of chemicals, and the use of maintenance workers who were older, with past asbestos work and longer smoking histories.

Since titanium tetrachloride is rapidly hydrolyzed in the presence of water, some of the pulmonary depositions in occupationally exposed workers may be due to some titanium tetrachloride hydrolysis products. In a study of 3 workers who worked for 9-10 years in a titanium dioxide processing factory, electron microscopy, and spectrometric and spectrographic analyses of lung tissue showed the presence of considerable amounts of some form of titanium (Elo et al. 1972). Electron-microscopy first identified 0.1-0.4-μm-diameter black particles in lysosomes of phagocytic cells filling the alveolar lumen. The black particles were very similar to the titanium dioxide particles that were layered on top of the grid and examined under the electron microscope, and further spectrographic analyses using X-ray fluorescence confirmed the presence of some form of titanium. Large quantities of some form of titanium were also present in the lymph nodes. Similar findings were made in the case of a

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55-year-old man who worked for 3 years in a titanium pigment processing factory (Ophus et al. 1979). He died of lung metastasis from an undifferentiated tumor in the right ileal bone. Because of his work history, his lungs were analyzed for the presence of titanium as well. Macroscopic and microscopic examinations revealed large amounts of white, birefractive pigment in all parts of the lungs without obvious fibrotic changes. Further analysis confirmed the presence of titanium and occasionally iron, and also showed that the crystal modification of titanium was in the form of rutile, a natural mineral of titanium dioxide that also contains some iron. Ash weight determinations of lung tissue revealed an increased concentration of titanium-containing dust particulates in the right middle lobe (43.3-49%) and lower lobe (39.2-47%) as compared to < 0.2% found in 2 control specimens. The absence of any pulmonary response to the deposits of titanium dust may be due to the fact that rutile is a biologically relatively inert crystalline form of titanium dioxide. None of the techniques used in this study can unequivocally identify the presence of titanium dioxide. In a study of a 45-year-old man who worked for 13 years as a furnace feeder in an aluminum smelting company, scanning electron microscopy and energy dispersive x-ray analysis showed that the lung tissue biopsy from the lower right lobe contained 1.39×10^9 exogenous particulates/cm^3 of tissue (Redline et al. 1986). The particulates contained various metallic alloys; 6 1% of the particulates consisted of aluminum and other metals such as titanium, zinc, and nickel; 35% contained various aluminum silicates; and 2% of the particles were silica. This finding confirms the possibility of titanium deposition in the lung tissue and, in this case, raises the possibility that there is an association of granulomatous lung disease with deposition of particles of titanium dioxide. The results of these three case reports indicate that titanium dioxide can be deposited in the lungs of occupationally exposed workers, and that these deposits may or may not cause histopathological changes. Further studies are needed to establish the causal relationship, if any, between deposits of titanium dust particulates and granulomatous lung disease.

Findings in animals support the observations made in humans. Female Sprague-Dawley rats were exposed by inhalation to 1,466, 5,112, 7,529, or 11,492 mg/m^3 of titanium tetrachloride for 10 minutes (Karlsson et al. 1986). None of the animals died from exposure, but signs of toxicity included wet noses, nasal discharge, swollen eyelids, and dyspnea. These signs disappeared 48-72 hours after exposure, and lung histopathology done 7 days later showed minor lesions. The lungs in 1 of 3 and 2 of 2 rats exposed to 5,112 and 11,492 mg/m^3, respectively, showed discrete inflammatory residues, thickened alveolar septa, and a sparse accumulation of phagocytes. Similar observations were made in other acute studies in rats (DuPont 1980). In a 4-week inhalation study, rats exposed intermittently to 5 mg/m^3 of hydrolysis products of titanium tetrachloride showed a mild dust-cell reaction and

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increased relative lung weight (DuPont 1979). In addition to increased lung weight, higher exposure concentrations (10 and 40 mg/m^3) induced concentration-related inflammation of the respiratory tract. The effects were described as acute bronchiolitis, interstitial pneumonitis, proliferation of alveolar cells, and hyperplasia of the tracheal epithelium with increased mucus secretion. These effects gradually disappeared during a recovery period of up to 12 months that followed exposure, although slight collagenized fibrosis persisted in the respiratory bronchioles and adjoining alveolar walls. The 5 mg/m^3 exposure level is considered a less serious LOAEL and was used to derive an intermediate-duration inhalation MRL of 0.01 mg/m^3, as described in the footnote in Table 2-l.

In a chronic inhalation study, groups of 100 Crl:CD rats/sex/concentration were exposed by inhalation to 0, 0.1, 1.0, and 10.0 mg/m^3, respectively, of atmospherically hydrolyzed titanium tetrachloride for 6 hours per day, 5 days per week for 104 weeks (EPA 1986; Lee et al. 1986). 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. The primary clinical finding was an increased incidence of irregular respiration and abnormal lung noises in exposed animals. The incidence was concentration-related (8, 12, 24, and 36% in males and 8, 16, 44, and 41% in females at 0, 0.1, 1.0, and 10.0 mg/m^3, respectively). Also, the time to first observation was shorter at higher concentrations. The major health effects of exposure to titanium tetrachloride were observed in the respiratory tract of exposed rats. The incidence of rhinitis increased with concentration and duration of exposure. In the control animals, the incidence ranged from 3.9 to 31.6% and was usually higher at 2 years. In the low-concentration group, the incidence of rhinitis at 1 year ranged from 4.3 to 15%, and at 2 years it ranged from 21.9 to 64.4%. In the mid- and high-concentration groups, the incidences were 4.5-31.8% and 25-33.3%, respectively, at 1 year, and 16.9-56.2% and 23.2-65.8%, respectively, after 2 years of exposure. Tracheitis also increased with duration and, to a lesser degree, with concentration. The two highest groups had an increased incidence of tracheitis as early as 3 months; after 2 years, tracheitis was increased in the lowest exposure group. The incidences of tracheitis at the end of the 2 years tiere 0-2.5%, 12-20%, 41-49%, and 30-44% for the control, low-, mid-, and high-exposure groups, respectively. The 0.1 mg/m^3 level 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. Mean absolute and relative lung weights were increased significantly (p< 0.05) after 1 and 2 years of treatment compared to untreated controls. In male rats, but not females, relative lung weight was increased significantly

(p< 0.05) after 6 months of treatment. Foci laden with yellow titanium tetrachloride hydrolysis product were present on the lung pleural surface and on the slightly enlarged tracheobronchial lymph nodes in the mid- and high-exposure groups. The pulmonary response in these two groups also included the presence of the dust-laden macrophages and hyperplasia of the alveolar lining. The incidence and severity of alveolar hyperplasia increased with concentration; incidences were 0% in the control and low-exposure groups, and 32-63% and 92-97% in the mid- and high-exposure groups, respectively. The concentration of 0.1 mg/m^3 is considered a LOAEL for the pulmonary effects and was used for the derivation of a chronic inhalation exposure MRL of 0.0001 mg/m^3, as described in the footnote in Table 2-l.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to titanium tetrachloride.

No histopathological alterations were reported in the heart and aorta from male rats (females were not tested) exposed to up to 40 mg/m^3 titanium tetrachloride aerosol 6 hours per day, 5 days per week for 4 weeks (DuPont 1979). No further information was provided.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to titanium tetrachloride.

No compound-related alterations were observed in the esophagus, stomach, duodenum, jejunum, cecum, and colon from male rats (females were not tested) exposed to up to 40 mg/m^3 titanium tetrachloride aerosol 6 hours per day, 5 days per week for 4 weeks (DuPont 1979). No further information was provided.

Hematological Effects. Limited information is available regarding hematological effects in humans following inhalation exposure to titanium tetrachloride. No abnormal values for hemoglobin, white blood cells, rieutrophils, monocytes, and basophils were found in 10 workers exposed for 4-17 years to low levels of titanium tetrachloride fumes (Lawson 1961). The level of titanium tetrachloride in the fumes was not reported. Three of the workers had mild eosinophilia, and four had relative lymphocytosis. Since there were no data from control subjects, it is difficult to estimate whether these changes are significant or not. According to the author, the observed lymphocytosis may have been caused by the influenza present among the workers at the time of the study. Another

limitation of the study is the lack of a detailed description of the other chemicals to which the workers may have been exposed.

No significant hematological alterations were reported in rats exposed intermittently for 4 weeks to up to 40 mg/m^3 titanium tetrachloride (DuPont 1979). Parameters evaluated included red cell count, total and differential white cell count, hemoglobin, hematocrit, mean cell volume, and mean corpuscular hemoglobin concentration. In a chronic inhalation exposure study, Crl:CD rats were exposed to 0, 0.1, 1.0, and 10.0 mg/m^3 of titanium tetrachloride 6 hours per day, 5 days per week for 2 years (EPA 1986; Lee et al. 1986). After 18 months of exposure, high-dose rats had a significant increase in neutrophils (p< 0.05) and a decrease in lymphocytes. Males at this concentration had a significant decrease in erythrocytes and significant increases in mean cell volume and mean cell hemoglobin.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to titanium tetrachloride.

Limited information is available regarding hepatic effects in animals. No histopathological effects were observed in the liver from male rats (females not tested) exposed to up to 40 mg/m^3 titanium tetrachloride aerosol 6 hours per day, 5 days per week for 4 weeks (DuPont 1979). This finding was consistent with the fact that the activities of serum transaminases were not significantly altered by the experimental treatment.

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to titanium tetrachloride.

Limited data are available regarding renal effects in animals after inhalation exposure to titanium tetrachloride. In male rats (females were not tested), exposure to 10 or 40 mg/m^3 of an aerosol of titanium tetrachloride 6 hours per day, 5 days per week for 4 weeks resulted in decreased urine osmolality and increased urine pH on the last day of exposure (DuPont 1979). These pai-ameters returned to pre-exposure levels after a 2-week recovery period. An exposure level of 5 mg/m^3 was without effect. The biological significance of these findings is unknown.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to titanium tetrachloride.

No compound-related histopathological alterations were observed in the thyroid, parathyroid, and pancreas from male rats (females were not tested) exposed 6 hours per day, 5 days per week for 4 weeks to up to 40 mg/m^3 titanium tetrachloride aerosol (DuPont 1979). No further information was provided.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation exposure to titanium tetrachloride.

The only information available regarding dermal effects in animals is that no histopathological alterations were observed in the skin from male rats (females were not tested) exposed 6 hours per day, 5 days per week for 4 weeks to up to 40 mg/m^3 titanium tetrachloride aerosol (DuPont 1979). No further information was provided.

Ocular Effects. Mild symptoms of toxicity developed in a case in which three research workers were accidentally exposed to titanium tetrachloride fumes (Ross 1985). One person developed eye irritation that lasted about two hours. Upon medical examination several hours after the accident, no abnormalities were found. In another case of accidental exposure, a 50-year-old chemical engineer was sprayed over his head, chest, neck, and back with titanium tetrachloride (Park et al. 1984). When he removed his mask to clean himself, he was exposed to vapor formed when titanium tetrachloride came in contact with air. He developed erythema of the conjunctivae, tongue, and pharynx with other signs of respiratory toxicity. His ocular symptoms were more severe than the ones described in the first case, possibly due to the formation of hydrochloric acid, which caused second- and third-degree bums over the parts of his body that came in contact with titanium tetrachloride. No information was given about the dose or the course of his eye injury.

Eye injury after titanium tetrachloride exposure was also observed in acutely exposed rats. Female Sprague-Dawley rats exposed to concentrations of 1,466, 5,112, 7,529, and 11,492 mg/m^3 of titanium tetrachloride for 10 minutes (Karlsson et al. 1986) had swollen eyelids, irritation, wet noses, nasal discharge, and dyspnea. Although the animals were observed for 7 days, the symptoms disappeared within 48-72 hours. No animals died from the exposure. Corneal opacity, necrotic keratitis, and conjunctivitis were reported in rats exposed to lethal concentrations of titanium tetrachloride for 2-240 minutes (DuPont 1980). No histopathological alterations were observed in the eyes of male rats

(females not tested) exposed to up to 40 mg/m^3 titanium tetrachloride 6 hours per day, 5 days per week for 4 weeks (DuPont 1979).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to titanium tetrachloride.

Information about animals is limited. Surviving rats exposed to median lethal concentrations of titanium tetrachloride hydrolysis products for 2-240 minutes exhibited weight loss (unquantified) after exposure (DuPont 1980). In a 4-week study, male rats exposed to 40 mg/m^3 titanium tetrachloride 6 hours per day, 5 days per week showed a 19% reduction in body weight gain relative to controls during the exposure period (DuPont 1979). However, the weight gain returned to a normal pattern during a post-exposure recovery period. Lower exposure levels, 5 or 10 mg/m^3, did not alter body weight gain. Body weight from Crl:CD rats exposed to 0, 0.1, 1.0, and 10.0 mg/m^3 of titanium tetrachloride 6 hours per day, 5 days per week for up to 2 years were not altered by the experimental treatment (EPA 1986; Lee et al. 1986).

2.2.1.3 Immunological and Lymphoreticular Effects

Very limited information is available regarding immunological effects in humans or animals following inhalation exposure to titanium tetrachloride. An elevated lymphocyte count of 23,700 cells/mm^3 was found in a worker after an accidental exposure to titanium tetrachloride (Park et al. 1984). No further information or details of exposure were provided, but the worker also suffered second- and third degree bums related to exposure over 25% of his body. In another study, 4 of 10 workers chronically exposed to low levels of titanium tetrachloride fumes had relative lymphocytosis (Lawson 1961). However, it is difficult to interpret this finding because no controls were available, and there was influenza among the workers at the time the study was conducted.

The immune status in humans is most commonly evaluated by *in vitro* testing of peripheral blood lymphocytes (PBLs). Impaired cellular immune function was found in a 45-year-old man who worked for 13 years as a furnace feeder in an aluminum smelting company (Redline et al. 1986). The *in vitro* responses of his PBLs to selected mitogens (phytohemagglutinin, pokeweed mitogen, and concanavalin A) were below the mean values for normal responses established in 50 control subjects. Since he presented with pulmonary granuloma containing different particles, his PBLs were tested 4 times over

an 1l-month period for responsiveness to titanium tetrachloride, nickel sulfate, and aluminum chloride. This was done to establish a possible causal relationship between the particulates in the pulmonary granuloma and the immune response of the delayed hypersensitivity type. Only the response to titanium tetrachloride was positive in two out of four tests. The controls used in the experiment were 3 painters exposed to titanium dioxide-based paints for 15-28 years; their response to all 3 metallic salts was negative. These results indicate that chronic exposure to titanium in this one patient may have led to his sensitization and may be related to the pulmonary granulomatous disease that he developed. However, three other chronically exposed individuals used as controls were not sensitive to titanium tetrachloride. The limitations of the study are that exposure occurred to several metals, that the dose or precise duration are not known, that the *in vitro* response of the patient to titanium tetrachloride was positive in two out of four tests, and most importantly, the use of inappropriate controls.

No histopathological alterations were observed in the thymus and spleen from rats exposed to up to 40 mg/m^3 titanium tetrachloride 6 hours per day, 5 days per week for 4 weeks (DuPont 1979). No further immunological parameters were evaluated in this intermediate-duration study. In a chronic inhalation study, Crl:CD rats were exposed to 0, 0.1, 1.0, and 10.0 mg/m^3 of hydrolyzed titanium tetrachloride for 6 hours per day, 5 days per week for 2 years (EPA 1986; Lee et al. 1986). The study focused on lung injuries and revealed the presence of two types of macrophages in the lung alveoli. Both types contained particles; one type had densely aggregated particles (dust-laden macrophages), and the other contained a small amount of particles (foamy dust macrophages). The incidence of these latter macrophages was increased in rats receiving 10.0 mg/m^3 of hydrolyzed titanium tetrachloride. Dose-related changes observed in the tracheobronchial lymph nodes of rats exposed to 1.0 and 10.0 mg/m^3 included slight enlargement of the nodes and foci laden with yellow titanium tetrachloride hydrolysis product. These tracheobronchial lymph nodes were also slightly enlarged. The two types of macrophages seen in treated rats were not present in any of the control animals. The results indicate that compound-related lung injury evoked an immune reaction in the form of increased macrophage infiltration. The limitations of the study are that other immune functions Were not tested and that no information is available regarding the numbers of lymphoid cells. It is therefore difficult to estimate the extent of immunologic injury in rats following chronic inhalation exposure to titanium tetrachloride.

All NOAEL and LOAEL values from each reliable study for immunological effects in rats in chronicduration studies are recorded in Table 2-l and plotted Figure 2-l.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to titanium tetrachloride.

Data regarding neurological effects in animals are limited to a report in which no histopathological alterations were observed in the brain from rats exposed to up to 40 mg/m^3 titanium tetrachloride 6 hours per day, 5 days per week for 4 weeks (DuPont 1979). Because no further neurological parameters were evaluated, this exposure level is not a reliable NOAEL; therefore, it is not presented in Table 2-l or Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to titanium tetrachloride.

Information regarding reproductive effects in animals was limited to a 4-week study which reported no histopathological alterations in the testis and epididymis from rats exposed 6 hours per day, 5 days per week to up to 40 mg/m^3 titanium tetrachloride (DuPont 1979). Female rats were not tested in this study. The 40 mg/m^3 exposure level is not considered a reliable NOAEL since no further reproductive end points were evaluated and females were not tested; therefore, this level is not presented in Table 2- 1 or Figure 2-l.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to titanium tetrachloride.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to titanium tetrachloride. Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A few epidemiological studies have examined cancer mortality in workers employed in industries using titanium tetrachloride. No association between titanium tetrachloride exposure and lung cancer mortality was found in 969 male workers occupationally exposed to <0.5->3.0 mg/m^3 of titanium tetrachloride for periods up to more than 5 years (EPA 1990b; Fayerweather et al. 1992). Of these workers, 24 lung cancer cases and 96 controls were included in the statistical analyses. Data on the incidence of lung cancer and chronic respiratory disease (from 1956 through 1985) and mortality (from 1935 through 1983) were included in the study. The smoking status, year of birth, and year of hire of the workers were also taken into account. No titanium tetrachloride exposure monitoring data were available before 1975, and the use of respirators for protection against titanium tetrachloride during routine operations was introduced in 1984. Statistical analysis of the available mortality and lung cancer incidence data showed that there was no association between titanium tetrachloride and lung cancer mortality (odds ratio, 1.1). The results showed that only cigarette smoking was a strong predictor of lung cancer mortality. The distribution of case and control subjects by three different exposure indices (exposure duration, time-weighted average exposure, and cumulative exposure index) showed no remarkable differences in frequencies by level of exposure. According to the investigators (Fayerweather et al. 1992), the finding of no association should not be interpreted as definitive because the statistical power of the study was limited and, the possibility that misclassification of exposure may have produced a bias toward finding no association.

Although lung squamous cell carcinoma and keratinizing squamous cell carcinoma were observed in rats chronically exposed to titanium tetrachloride, it is difficult to estimate their relevance to lung tumors in humans (EPA 1984, 1986; Lee et al. 1986). One hundred male and 100 female Crl:CD rats were exposed to 0, 0.1, 1.0, and 10.0 mg/m^3 of hydrolyzed titanium tetrachloride vapors 6 hours per day, 5 days per week for 104 weeks (2 years). Chronic toxicity was evaluated by sacrificing 20 rats per group at 3, 6, and 12 months. Histopathology was done on all major tissues and organs, and no changes were observed except in the respiratory tract. Two types of lung squamous cell carcinoma

were found. Well-differentiated squamous cell carcinoma was found in 1 of 75 males and 2 of 75 females exposed to 10.0 mg/m^3 of titanium tetrachloride (EPA 1984). The other lung tumor type was a keratinized, cystic, squamous cell carcinoma found in 1 of 75 males and 1 of 75 females from the same exposure group. No tumors were present in the lower exposure groups or in the controls. The results of this study were also reported elsewhere (EPA 1986; Lee et al. 1986). No abnormal clinical signs, changes in body weights, or excess mortality were observed in any of the exposed groups. Histopathology revealed no changes in the thyroid, adrenal glands, testes, kidneys, or other organs (not specified). The results showed that the only compound-related changes occurred in the lungs and thoracic lymph nodes. Morphological analysis of the exposure vapors revealed fine, round, transparent particles (<1 μm in diameter) and large aggregated particles (up to 400 μm in diameter). Energy-dispersive X-ray analysis of the particulates showed two peaks characteristic of titanium and chlorine. Although it is the same set of animals as in the EPA (1984) study, the incidence of lung squamous cell carcinomas was reported differently in this report. The total number of lung carcinomas was 5 (2 of 69 males and 3 of 74 females), the same as the total in the EPA (1984) study. Three of the five were microscopic-sized well-differentiated lung squamous cell carcinomas, and two were keratinized cystic squamous cell carcinomas. The carcinomas occurred in the alveoli with squamous metaplasia and next to the alveolar ducts with aggregated dust-laden macrophages and were probably a result of chronic tissue irritation from dust-laden macrophages and cellular debris. No metastases were found in any of the rats. According to the authors (Lee et al. 1986), these lung carcinomas are a unique type of experimentally induced tumors that are not known to occur in humans or other animals. Their etiology is also different from human squamous cell carcinoma. Lung squamous cell carcinomas in humans arise in the basal cells of the bronchial epithelium, while cystic keratinizing squamous cell carcinomas observed in this study developed from the alveolar lining cells that are close to the alveolar duct region. It is, therefore, difficult to determine the relevance of these keratinizing carcinomas to humans. In a recent written communication, DuPont (1994) stated that the lung lesions observed in rats by Lee et al. (1986) were reexamined and the conclusion was that three of the lesions should be diagnosed as squamous metaplasia and the other two as proliferative 'keratin cysts. This reevaluation was consistent with the opinion of an international panel of 13 pathologists who examined similar lung lesions in rats caused by exposure to titanium dioxide. The panel agreed that the lesions were not malignant neoplasms; a majority of the members agreed that the lesions were not neoplastic.

2.2.2 Oral Exposure

No studies were located regarding the following health effects in humans or animals after oral exposure to titanium tetrachloride:

2.2.2.1 Death

2.2.2.2 Systemic Effects

2.2.2.3 Immunological and Lymphoreticular Effects

2.2.2.4 Neurological Effects

2.2.2.5 Reproductive Effects

2.2.2.6 Developmental Effects

2.2.2.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to titanium tetrachloride.

2.2.3 Dermal Exposure

When occupational exposures occur, both air passages and the skin are open to attack.   Therefore, many of the findings described in the inhalation section will be repeated in this section.

2.2.3.1 Death

One death was reported in the case of a worker who was accidentally splashed over his whole body with titanium tetrachloride (Chitkara and McNeela 1992). He suffered extensive burns to facial skin, nasopharynx, and larynx, and both his eyes were severely injured. His corneas were thick and opaque with extensive swelling of the bulbar conjunctiva and episclera. Over the next 14 days, some of the opacity in the right eye cleared, but there was no improvement in the left eye. The patient died from the complications of severe pulmonary injury caused by inhalation of titanium tetrachloride fumes.

No increase in mortality from any cause was reported in workers occupationally exposed to titanium tetrachloride from 1 day to over 5 years (EPA 1990b; Fayerweather et al. 1992). The studies are limited, however, because they usually do not report the dose or duration of exposure, because they are focused somewhat on the mortality from lung cancer, and because of the potential exposure of the subjects to other chemicals in the chemical manufacturing complex.

No studies were located regarding death in animals after dermal exposure to titanium tetrachloride.

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, hematological, hepatic, or renal effects in humans or animals after dermal exposure to titanium tetrachloride. The systemic effects observed after dermal exposure are discussed below.

Respiratory Effects. Only mild adverse pulmonary effects were observed in workers following an accidental exposure to titanium tetrachloride (Ross 1985). The precise concentration and duration of exposure are not known. The mild symptoms included ticklish cough and tightness in the chest that both lasted about two hours. Chest X-rays performed several hours later did not reveal any abnormalities. The lungs are the target organ for titanium tetrachloride exposure. A 45year-old man who worked for 13 years as a furnace feeder in an aluminum smelting company was diagnosed with granulomatous lung disease (Redline et al. 1986). The scanning electron microscopy and energy dispersive X-ray analysis of his lung tissue biopsy showed that the lower right lobe contained 1.39×10^9 exogenous particulates/cm^3 of tissue. Further analysis showed that the particulates contained various metallic alloys: 61% of the particulates consisted of aluminum and other metals such as

titanium, zinc, and nickel; 35% contained various aluminum silicates; 2% of the particles were silica. This finding confirms the possibility of titanium deposition in the lung tissue, and in this case raises the possibility that there is an association between granulomatous lung disease with metal containing particle deposition. It is also possible that these deposits cause local pulmonary tissue irritation, which can progress to granulomatous lung disease. Further studies are needed to establish a causal relationship between deposits of titanium dust particulates and granulomatous lung disease.

No studies were located regarding respiratory effects in animals after dermal exposure to titanium tetrachloride.

Dermal Effects. Titanium tetrachloride is a highly corrosive acute irritant to the skin, eyes, mucous membranes, and respiratory tract (EPA 1985b). In a study of acute accidental occupational exposure to liquid titanium tetrachloride, three workers suffered chemical and thermal skin injuries from the treatment that followed their exposure (Lawson 1961). The precise dose and duration of exposure were not known, but all three workers were extensively sprayed with water, which was a contraindicated treatment. The corrosive and thermal dermal injuries did not come from titanium tetrachloride alone but resulted from the heat generated by the reaction of titanium tetrachloride and water. This extremely vigorous reaction is exothermal, generating large quantities of heat and producing hydrochloric acid responsible for the highly corrosive dermal effects. Therefore, the titanium tetrachloride hydrolysis resulted in the third-degree bums in all three workers. In all three cases, the most severe bums occurred in areas that were occluded by either belts or shoes. The bums were deep, occasionally required skin grafting, and took a long time to heal. In all three cases the scars were surrounded by dark-brown pigmentation of unknown origin/cause or chemical makeup. Nine additional cases with less severe outcomes were also noted but were not described in this report. The effects ranged from mild second-degree bums to transitory erythema. It is postulated that the initial thermal bum exposes the deeper tissue layers to the effects of hydrochloric acid, resulting in more severe bums than either one would cause alone (Chitkara and McNeela 1992).

To test for the effects of titanium tetrachloride on skin under controlled conditions, 10 volunteers were exposed dermally to 0.5 mL of purified anhydrous titanium tetrachloride for 1 minute (Lawson 1961). Assuming that the chemical was 100% pure, the concentration would be 860 mg, or 12.3 mg/kg/day of titanium tetrachloride. It was not possible to remove all the chemical by wiping the skin with dry towels; a whitish-yellow granular deposit was still present on the site of exposure. This remaining

deposit was washed off with cold water. In this experiment, the subjects reported a stinging sensation between 5 and 32 seconds after exposure. This sensation disappeared after washing with cold water. According to the author, the experiment confirmed that the titanium tetrachloride dermal injury must be treated as a combination thermal-acid bum, as has been observed in previous cases of accidental exposure (Lawson 1961).

It has been postulated that harmful effects of titanium tetrachloride are due to its extremely vigorous reaction with water in any form (perspiration on the skin, tears, moisture in the air) resulting in liberation of large quantities of heat. The mechanism of injury is thought to involve a thermal bum, which then exposes the deeper tissue layers to other titanium tetrachloride hydrolysis products such as hydrochloric acid, resulting in even more severe and deeper bums. In other words, the extremely serious effects observed following exposure to titanium tetrachloride are the result of combined thermal and acid bums (Chitkara and McNeela 1992).

Application of undiluted titanium tetrachloride with a cotton swab to the clipped skin of guinea pigs resulted in necrosis with erythema after the fifth application (DuPont 1994). The injury was similar to a second-degree thermal bum. No further information was located regarding dermal effects in animals after dermal exposure to titanium tetrachloride.

Ocular Effects. In a case of acute accidental exposure, three research workers were exposed to titanium tetrachloride fumes and suffered minor symptoms (Ross 1985). The workers were using titanium tetrachloride to assess a welding torch when a brass tap flew off, spilling liquid titanium tetrachloride, and filling the 8.5x17-foot room with fumes. One of the workers developed a cough, tightness in the chest, and eye irritation. All these symptoms, which were considered mild, lasted for about 2 hours.

In cases of acute accidental eye exposure to liquid titanium tetrachloride, the injury to the eye depends on the degree of the bum and the treatment that follows (Chitkara and McNeela 1992).-In the description of eight cases of acute eye injury, the exposure concentrations were not reported. On the basis of these eight cases, four grades of eye bums were identified. Grade I and grade II eye bums resolve without complications, while grade III and grade IV bums result in eye loss. Grade I eye injuries usually consist of mild defects of inferior comeal and conjunctival epithelium that heal within 2-3 days after the exposure. Grade II injuries affect the same eye structures but are more severe and

take longer to heal. No information on grade III eye injuries was given. The grade IV eye injuries have cornea1 and conjunctival bums accompanied by conjunctival ischemia and lens opacity. Over a period of time (up to 2 months), this injury progresses to severe cornea1 stromal lysis and ultimately cornea1 perforation resulting in blindness (Chitkara and McNeela 1992).

No studies were located regarding ocular effects in animals after dermal exposure to titanium tetrachloride.

2.2.3.3 Immunological and Lymphoreticular Effects

There is limited information regarding immunological effects in humans following dermal exposure to titanium tetrachloride. An elevated lymphocyte count of 23,700 cells/mm^3 was found in a worker after an accidental exposure to titanium tetrachloride (Park et al. 1984). There was no information on the precise dose. This worker had suffered second- and third-degree exposure related bums over 25% of his body. Relative lymphocytosis was observed in 4 of 10 workers chronically exposed to low levels of titanium tetrachloride fumes (Lawson 1961). The relevance of this finding is not clear because there were no controls and there was influenza among the workers at the time the study was conducted. Based on these results, it is not clear if the lymphocytosis observed was an adverse effect of titanium tetrachloride exposure or not.

PBLs are commonly used in the assessment of the immune status in humans. Impaired cellular immune function was found in a 45year-old man who worked for 13 years as a furnace feeder in an aluminum smelting company (Redline et al. 1986). The *in vitro* response of his PBLs to selected mitogens (phytohemagglutinin, pokeweed mitogen, and concanavalin A) was below the mean values established in 50 control subjects. His PBLs were also tested 4 times over an 11-month period for responsiveness to titanium tetrachloride, nickel sulfate, and aluminum chloride. This was done to establish a possible causal relationship between the metal containing particulates in the pulmonary granuloma and the immune response of the delayed hypersensitivity type. All the responses were negative except for the response to titanium tetrachloride, which was positive in two out of four tests. The controls used in the experiment were 3 painters exposed to titanium-based paints for 15-28 years; their response to all 3 metallic salts was negative. These results indicate that chronic exposure to titanium in this one patient may have led to his sensitization. They also suggest that the accumulation of particulates with titanium in the lungs may be related to the pulmonary granulomatous disease that

this patient developed. However, the three other chronically exposed individuals used as controls were not sensitive to titanium. The limitations of the study are that the subject was exposed to several metals, that the dose and precise duration are not known, and that the in vitro response of the patient to titanium tetrachloride was positive in two out of four tests.

No studies were located regarding immunological effects in animals after dermal exposure to titanium tetrachloride.

No studies were located regarding the following health effects in humans or animals after dermal exposure to titanium tetrachloride:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans after dermal exposure to titanium tetrachloride. However, as stated at the beginning of Section 2.2.1, the relative amount of exposure by each route in studies of occupational exposure to titanium tetrachloride is not known. The incidences of cancer, chronic respiratory disease, pleural thickening/plaques, and pulmonary fibrosis were investigated from 1956 through 1985 in a group of 1,576 workers occupationally exposed to titanium dioxide (Chen and Fayerweather 1988). There were no monitoring data for titanium dioxide exposure prior to 1975. The time-weighted average (TWA) ranges for titanium dioxide exposure (by quartile) were: >O to < 5.0 mg/m^3, 5.0 to <10 mg/m^3, 10 to < 20 mg/m^3, and >20 mg/m^3. Exposure durations were not specified for individual workers; however, 25% of them were exposed for less than 0.2 years, 25% were exposed for between 0.2 and 1 year, 25% were exposed for between 1 and 4 years, and

25% were exposed for more than 4 years. Although the results indicate that both the incidence of cancer cases and the incidence of lung cancer specifically were slightly higher in titanium dioxide-exposed groups as compared to the control group (901 nonexposed workers), this increase was not statistically significant. Nested case-control analyses based on 16 lung cancers and 898 control subjects showed that there was also no statistically significant association between titanium dioxide exposure and risk of lung cancer after adjusting for age and exposure to titanium tetrachloride, pigmentary potassium titinate (PKT), and asbestos (Chen and Fayerweather 1988). Similar observations were made with respect to the incidence of lung cancer (based on 27 cases of lung cancer deaths and 331 noncancer decedent controls) and chronic respiratory disease (based on 88 chronic respiratory disease cases and 898 noncancerous nonrespiratory disease controls). No cases of pulmonary fibrosis were observed in any of the exposed workers. The results indicate that exposure to titanium dioxide was not associated with an increased incidence of lung cancer. These results are important for two reasons: titanium dioxide is one of the hydrolysis products of titanium tetrachloride, and the results support the observations made regarding the incidence of lung cancer among titanium tetrachloride-exposed workers discussed in Section 2.2.1.2 (EPA 1990b; Fayerweather et al. 1992). The results indicate that exposure to titanium tetrachloride and exposure to its hydrolysis product, titanium dioxide, do not increase lung cancer incidence among exposed workers.

No studies were located regarding carcinogenic effects in animals after dermal exposure to titanium tetrachloride.

2.3 TOXICOKINETICS

No studies were located regarding absorption, distribution, metabolism, or excretion of titanium tetrachloride in humans or animals following exposure to titanium tetrachloride. Because of the physicochemical characteristics of titanium tetrachloride, the major route of exposure is by inhalation, and the major target organ is the lung. Exposure can also occur by the dermal route, especially in cases of accidental .occupational exposures. Although there are no studies on absorption or distribution by any of the three routes, it was shown that particles of titanium (titanium dioxide) are present in the lungs of titanium tetrachloride occupationally exposed individuals (Elo et al. 1972; Ophus et al. 1979; Redline et al. 1986).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption in humans or animals following inhalation exposure to titanium tetrachloride. However, particles (presumably of titanium dioxide) were detected in the liver and spleen from rats exposed to 10 mg/m^3 titanium tetrachloride aerosol 6 hours per day, 5 days per week for 2 years suggesting that absorption of titanium occurred (Lee et al. 1986). It is well known, however, that particles are swallowed after being expelled from the respiratory tract by mucocilliary clearance.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans or animals after oral exposure to titanium tetrachloride.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to titanium tetrachloride.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans following inhalation exposure to titanium tetrachloride. However, in a case report of chronic inhalation exposure to titanium dioxide, which is one of the titanium tetrachloride hydrolysis products, particles similar to titanium dioxide were found in lysosomes of phagocytes within the alveolar lumen (Elo et al. 1972). Spectrometric and spectrographic analysis showed accumulation of titanium dioxide in the lungs. Analysis of tissues from one worker who drowned 4 months after stopping work showed that titanium was also present in the lymph nodes adjacent to the lung. No titanium was found in the tissue specimens from brain, thyroid gland, myocardium, spleen, liver, kidneys, and nerve ganglia of the sympathetic trunk. These results suggest that titanium selectively accumulates in the lung and adjacent lymph nodes, but

additional studies are needed to show that this accumulation occurs also after exposure to titanium tetrachloride.

Very limited information was available regarding distribution of titanium tetrachloride in animals following inhalation exposure. Dust particles, presumably from titanium tetrachloride, were observed in the liver and spleen from rats exposed to 10 mg/m^3 titanium tetrachloride aerosol 6 hours per day, 5 days per week for 2 years (Lee et al. 1986). It is well known, however, that inhaled particles are swallowed after being expelled from the respiratory tract via mucocilliary clearance.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans or animals after oral exposure to titanium tetrachloride.

2.3.2.3 Dermal Exposure

In a case study of accidental occupational exposure to titanium tetrachloride, three workers suffered third-degree bums because they were extensively sprayed with water following the exposure (Lawson 1961). The wounds took a long time to heal, and in all three workers the scars were surrounded by dark brown pigmentation. The authors suggested that the pigmentation may have been due to the titanium deposits.

2.3.3 Metabolism

No studies were located regarding metabolism in humans or animals following inhalation, oral, or dermal exposure to titanium tetrachloride.

2.3.4 Elimination and Excretion

No studies were located regarding excretion in humans or animals following inhalation, oral, or dermal exposure to titanium tetrachloride.

2.4 MECHANISMS OF ACTION

The chemical properties of titanium tetrachloride are responsible for effects observed following both inhalation and dermal exposures. The instability of titanium tetrachloride in the presence of water leads to its rapid hydrolysis, which generates heat and various hydrolysis products. One of these hydrolysis products, hydrochloric acid, is partially responsible for the corrosive effects observed following exposure to titanium tetrachloride. In a study that compared the effects of titanium tetrachloride and hydrochloric acid in mice after acute inhalation exposure, it was concluded that an active component in both cases was hydrochloric acid (Mezentseva et al. 1963). The results showed that 9 of 15 mice exposed to titanium tetrachloride, and 1 of 15 mice exposed to hydrochloric acid, died. One possible explanation for the more severe effects seen from exposure to titanium tetrachloride compared with hydrochloric acid is that hydrochloric acid, because of its high solubility, is dissolved in the moisture of the nasopharynx and trachea, and thus penetrates the lungs to only a very limited extent. However, in the case of exposure to titanium tetrachloride, the hydrolysis occurs in several steps; one of the hydrolysis products, titanium oxide hydrate, is a particulate that can adsorb some of the hydrochloric acid vapors that are also generated during hydrolysis and carry them into the deeper parts of the lungs. In the lungs, intermediate hydrolysates continue the hydrolysis process with the further release of hydrochloric acid, resulting ultimately in larger amounts of hydrochloric acid being carried deeper in the lung and alveoli (Mezentseva et al. 1963). This study is limited in that the precise exposure levels are not known, since the titanium tetrachloride concentrations were communicated as separate titanium concentrations and hydrochloric acid concentrations. The study also did not give detailed information on the exposed animals.

No studies were located regarding the mechanism of action of titanium tetrachloride in humans or animals after oral exposure.

As in the case of inhalation injuries, the harmful effects of titanium tetrachloride to the skin and the eyes are partly due to its extremely vigorous reaction with water in any form (perspirati'dn on the skin, tears, moisture in the air) resulting in the generation of heat. The mechanism of injury involves a thermal burn, which exposes the deeper tissue layers to hydrolysis products of titanium tetrachloride such as hydrochloric acid, resulting in even more severe and deeper bums. In other words, the extremely serious effects observed following exposure to titanium tetrachloride are the result of combined thermal and acid bums (Chitkara and McNeela 1992).

2.5 RELEVANCE TO PUBLIC HEALTH

The major and most common exposures to titanium tetrachloride are via the inhalation and dermal routes. Titanium tetrachloride is not stable and undergoes rapid hydrolysis. In the presence of water, titanium tetrachloride is hydrolyzed through a vigorous exothermic reaction generating a large quantity of heat and several hydrolysis products, including hydrochloric acid. Therefore, exposure can cause thermal and chemical burns in humans and animals. Monitoring data for titanium tetrachloride in environmental media are non-existent, and its chemical properties suggest that titanium tetrachloride partitions to the air. Therefore, the most likely route of human exposure to titanium tetrachloride hydrolysis or its intermediate products is inhalation.

The most significant effects of acute, intermediate, or chronic inhalation exposure to titanium tetrachloride are mild-to-severe pulmonary injuries. The corrosive effects of acute exposure can also affect the skin, eyes, and the mucous membranes of the upper respiratory tract. These effects have been observed in humans and animals. Since the cases of acute or chronic exposure in humans are usually accidental or occupational and the precise exposure concentrations are not known, it has not been possible to measure the dose-response relationship to any degree of accuracy. However, the results of both acute and chronic exposure in animals suggest that adverse respiratory effects in animals are dose-dependent. The eye injuries resulting from acute dermal exposure to titanium tetrachloride in humans have been assigned to four degrees of severity indicating that they are time and concentration-dependent. It is not known if the animal data support this finding because of the limited information available regarding eye injuries in animals. In cases of acute animal exposure to titanium tetrachloride vapor, only mild eye injuries such as eyelid swelling have been observed.

Very few studies have addressed the question of the mechanism of pulmonary toxicity and the role hydrochloric acid plays in it. The results of a study in mice showed that titanium tetrachloride was more toxic than hydrochloric acid. One possible explanation for the more severe effects seen from exposure to titanium tetrachloride compared with hydrochloric acid is that hydrochloric-acid, because of its high solubility, is dissolved in the moisture of the nasopharynx and trachea and thus penetrates the lungs to only a limited extent. However, in the case of exposure to titanium tetrachloride, the final hydrolysis product, titanium oxide hydrate, is a particulate that can adsorb some of the hydrochloric acid vapors that are generated during hydrolysis and carry them into the deeper parts of the lungs. In the lungs, the adsorbed hydrochloric acid is released from the particulate, resulting ultimately in

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hydrochloric acid being carried deeper into the lung and to the alveoli, thus causing tissue burns at a much deeper level than hydrochloric acid inhalation (Mezentseva et al. 1963). This mechanism of toxicity can also explain the second- and third-degree burns observed after acute dermal exposure to titanium tetrachloride.

Only one case of delayed toxic pulmonary effects was described in humans following acute inhalation exposure. The exposure caused severe toxic lung effects, but 5 weeks after exposure, fiberoptic bronchoscopy revealed erythema of the entire bronchial tree and the presence of 35-40 fleshy polypoid lesions. The presence of the polyps, according to the authors, was a sign of an exaggerated, but normal, reparative process of the tracheobronchial injury. This delayed complication has been seen in thermal respiratory injuries, indicating that the severe adverse respiratory effects seen in this case may, in part, be due to the exothermal nature of the titanium tetrachloride hydrolysis reaction. One year after the injury his lung appeared normal with some degree of mild stenosis.

The reported adverse hematological effects in humans following acute inhalation exposure include mild eosinophilia and possibly lymphocytosis. Because of the very limited database, it is difficult to assess the significance of these findings. These observations could not be verified in animal systems because of the lack of similar hematological effects following acute exposure (DuPont 1980). However, the results of chronic exposure in rats do not support the observations in humans. After 18 months of exposure, a significant increase in the number of neutrophils and a decrease in lymphocytes were observed in exposed rats. Resolution of these contradictory findings must await additional animal studies.

Insufficient information is available regarding adverse immunological effects in humans following titanium tetrachloride exposure. In an effort to elucidate the etiology of granulomatous lung disease, lymphocytes from a chronically exposed worker with the disease were tested for their responsiveness to titanium tetrachloride. The results were compared to those from three subjects chronically exposed to titanium-containing paints. The results were inconclusive because the response of the controls was always negative while the response of the patient was positive in two out of four tests done over an 1l-month period. The results of chronic inhalation exposure in rats indicate that compound-related lung injury evoked an immune response in the form of an increased macrophage infiltration. The limitation of the study is that other immune functions were not tested. As in the case of studies in

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humans, insufficient information is available to estimate the true extent of immunologic injury in rats following chronic inhalation exposure to titanium tetrachloride.

Since no toxicokinetic information is available on titanium tetrachloride, it is not possible to estimate if there is a potential for bioaccumulation of the compound in humans. Because of its chemical characteristics and rapid hydrolysis in the presence of water, however, it is unlikely that it would bioaccumulate in the body although its final hydrolysis product may do so.

It is not possible to assess the neurological, reproductive, or developmental effects in humans because no information was located regarding these effects in humans and only limited data were available in animals. The limited information available indicates that titanium tetrachloride is not genotoxic in bacteria (Kanematsu et al. 1980; Ogawa et al. 1987).

Of major concern to individuals occupationally exposed to titanium tetrachloride is potential acute exposure to large quantities of the compound via inhalation or dermal contact. The degree of respiratory or dermal injury depends greatly on the amount of titanium tetrachloride to which workers are exposed, the protective clothing they use, and the treatment measures undertaken after the exposure. The treatment should avoid the use of water until liquid titanium tetrachloride is wiped off with dry towels in order to prevent rapid hydrolysis of titanium tetrachloride and the generation of heat and hydrolysis products such as corrosive hydrochloric acid.

Since the major route of exposure to titanium tetrachloride is inhalation, the sensitive population includes persons with bronchitis, pneumoconiosis, bronchial asthma, pulmonary tuberculosis, and diseases of the upper respiratory tract (Mezentseva et al. 1963). For the same reason, work with titanium tetrachloride is contraindicated in persons who have other pulmonary or cardiovascular conditions that make it difficult for them to wear a protective mask (Mezentseva et al. 1963).

It is very unlikely that titanium tetrachloride would be found at hazardous waste sites because of its instability and rapid hydrolysis.

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Minimal Risk Levels for Titanium Tetrachloride.

Inhalation MRLs.

- An MRL of 0.01 mg/m^3 has been derived for intermediate inhalation exposure (15-364 days) to hydrolysis products of titanium tetrachloride.

The intermediate-duration inhalation MRL was based on a LOAEL of 5 mg/m^3 for mild lung dust cell reaction and increased relative lung weight observed in groups of 25 male rats exposed intermittently to 0, 5, 10, or 40 mg/m^3 for 4 weeks (DuPont 1979). Some alterations seen in the mid- and high-exposure groups consisted of acute bronchiolitis, interstitial pneumonitis, proliferation of alveolar cells, and hyperplasia of tracheal epithelium with hypermucous secretion. The extent and severity of these lesions were concentration-dependent and, for the most part, they disappeared during a recovery period of up to one year after exposure.

- An MRL of 0.0001 mg/m^3 has been derived for chronic inhalation exposure (365 days or more) to hydrolysis products of titanium tetrachloride.

The chronic-duration inhalation MRL was based on a LOAEL of 0.1 mg/m^3 for tracheitis and rhinitis seen in groups of 100 male and female Crl:CD rats exposed to 0.1, 1.0, or 10 mg/m^3 for up to 2 years (EPA 1986; Lee et al. 1986). An increased incidence of rhinitis was seen in the low-exposure group after 1 year. An increased incidence of tracheitis was not seen in the low-exposure group prior to 2 years of exposure. Adverse respiratory effects, including alveolar hyperplasia, were concentration dependent.

No acute-duration inhalation MRL has been derived for titanium tetrachloride because there are no adequate dose-response data available in humans or animals that identify threshold levels for noncancer health effects.

Oral MRLs.

No MRLs have been derived for oral exposure to titanium tetrachloride because there are no dose-response data available in humans or animals for any duration of exposure that identify threshold levels for noncancer health effects.

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Death. One death was reported in the case of a worker who was accidentally splashed over his whole body with titanium tetrachloride (Chitkara and McNeela 1992). He suffered extensive burns to facial skin, nasopharynx, and larynx, and both his eyes were severely injured. His corneas were thick and opaque with extensive swelling of the bulbar conjunctiva and episclera. Over the next 14 days, some of the opacity in the right eye cleared, but there was no improvement in the left eye. The patient died from the complications of severe pulmonary injury caused by inhalation of titanium tetrachloride fumes (Chitkara and McNeela 1992).

Except for the single case described above, no increase in mortality from any cause was reported in workers occupationally exposed to titanium tetrachloride for 1 day to over 5 years (EPA 1990b; Fayerweather et al. 1992). However, these studies are limited because they are focused somewhat on the incidence of, and mortality from, lung cancer, and because of the potential exposure of the subjects to other chemicals in the chemical manufacturing complex. Exposure to other chemicals confounds matching the controls and the exposed individuals.

Limited information exists regarding lethal effects of titanium tetrachloride in animals. A 4-hour inhalation LC_{50} of 460 mg/m^3 in rats was reported (DuPont 1980); death was attributed to pulmonary edema due to increased permeability of the damaged alveolar epithelium. In mice, single acute inhalation exposure to low, medium, and high levels of titanium tetrachloride and its hydrolysis products, titanium oxychloride and hydrochloric acid, caused dose-dependent death in 9 of 15 mice (Mezentseva et al. 1963). The study also shows that titanium tetrachloride was more lethal than hydrochloric acid, which was also used in the study. One possible explanation is that hydrochloric acid, because of its high solubility, dissolves in the moisture of the nasopharynx and trachea, penetrating the lungs to a very small extent. In the case of titanium tetrachloride exposure, the hydrolysis occurs in several steps, and at each step, the products can absorb the hydrochloric acid that is also generated during hydrolysis, and carry it into the deeper parts of the lungs. There the process is repeated, resulting ultimately in a larger amount of hydrochloric acid being carried deeper into the lung and to the-alveoli (Mezentseva et al. 1963). Two of 2.5 rats exposed to 40 mg/m^3 titanium tetrachloride intermittently for 4 weeks died on test days 15 and 23 (DuPont 1979). Death was attributed to respiratory failure. Gross and microscopic observations of the respiratory tract suggest that a combination of irritative effects (i.e., denuded tracheal epithelium) as well as physical obstruction of the tracheal lumen by dust particles may have contributed to the deaths.

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Systemic Effects.

Respiratory Effects. The lungs are the major target organ following inhalation exposure and to titanium tetrachloride. The case studies of humans acutely exposed to titanium tetrachloride fumes have shown the irritant nature of the inhaled chemical. Since titanium tetrachloride undergoes hydrolysis almost immediately when in contact with water or moisture in the air (forming fumes that contain titanium oxychloride and hydrochloric acid), its main effect on the lungs is corrosive, and although the degree of pulmonary injury can vary, it can result in intense chemical bronchitis or pneumonia (Lawson 1961). The mild irritant symptoms include cough and tightness in the chest, which last only a short time and usually leave no abnormalities visible on a chest X-ray (Ross 1985).

More severe pulmonary effects consisted of marked congestion of the mucous membranes of the pharynx, vocal cords, and trachea (Ross 1985). Although this exposure was acute, it had long-term effects that included stenosis of the larynx, trachea, and upper bronchi. In some cases of accidental exposure, these symptoms progressed to severe upper airway distress that required intubation and ventilation (Park et al. 1984). Additional symptoms may include hypoxia and diffuse pulmonary infiltrates suggestive of adult respiratory distress syndrome. The improvement is gradual, and may go through different stages. In one case of accidental exposure to titanium tetrachloride fumes, fiberoptic bronchoscopy performed 5 weeks after exposure revealed erythema of the entire bronchial tree and the presence of 3540 fleshy polypoid lesions (Park et al. 1984). The authors indicated the presence of the polyps was a sign of an exaggerated, but normal, reparative process of the tracheobronchial injury seen in thermal respiratory injuries. This delayed complication provides support to the theory that the severe adverse respiratory effects observed after exposure to titanium tetrachloride are in part due to the exothermal nature of the titanium tetrachloride hydrolysis reaction. Only some degree of mild pulmonary stenosis was evident in this case after 1 year. Impairment of the pulmonary function may result from chronic occupational exposure to significant levels of titanium tetrachloride. The results of occupational exposure of 209 workers employed in a metal reduction facility in Ashtabula, Ohio, were reported in two-retrospective studies (Garabrant et al. 1987; NIOSH 1980). The results suggest that pulmonary impairment may be caused by exposure to titanium tetrachloride. Of the 209 workers, 78 were engaged in the titanium tetrachloride reduction process and were also exposed to sodium, titanium dioxide, and titanium oxychloride. Logistic regression analysis of the chest radiograph data showed that pleural thickening was strongly related to the duration of work in titanium production (p<O.OOl). The initial estimates of loss of pulmonary function, taking smoking into account, was

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45 ml/year leading to a deficit of 1.8 L/40-year employment period (NIOSH 1980). Further analysis of the employees based on job and duration of employment also showed large decreases in FVC in workers employed in titanium tetrachloride reduction for at least 10 years (Garabrant et al. 1987). A regression analysis of the data adjusted for age, height, and smoking revealed that the rate of loss of FVC was 24 mL per year for the titanium tetrachloride workers (Garabrant et al. 1987). The results also showed an inconclusive relationship between previous asbestos exposure/cigarette smoking and pleural thickening. These results suggest that chronic exposure to titanium tetrachloride may result in restrictive pulmonary changes and that there is no clear association between pleural thickening and reduction in ventilatory capacity. It is difficult to determine the precise cause of these pulmonary abnormalities, because of the lack of information on the duration, route, exposure levels, and concomitant exposure to a mixture of chemicals.

Since titanium tetrachloride is rapidly hydrolyzed in the presence of water, it is not likely to be found in the body. However, it is likely that some of the pulmonary depositions in occupationally exposed workers are titanium dioxide. Indeed, considerable amounts of titanium were found in lung tissue of three workers who worked for 9-10 years in a titanium dioxide processing factory (Elo et al. 1972). Electron microscopy identified 0.l-0.4-μm-diameter titanium particles in lysosomes of phagocytic cells filling the alveolar lumen. Large quantities of titanium were also present in the lymph nodes. Similar findings were made in the case of a 55-year-old man who worked for 3 years in a titanium dioxide pigment processing factory (Ophus et al. 1979). Macroscopic and microscopic examinations revealed large amounts of white, birefractive pigment in all parts of the lungs without obvious fibrotic changes. Further analysis confirmed the presence of titanium and occasionally iron and also showed that the crystal modification of titanium found in the lung was rutile and thus likely to have come from the crude ore. The absence of any pulmonary response to the titanium dust deposits may be due to the fact that rutile is a biologically inactive crystalline modification of titanium/titanium dioxide. None of the techniques used in this study can unequivocally identify the presence of titanium dioxide. Particulate titanium was also present in the lungs of a 45year-old man who worked for 13 years as a furnace feeder in an aluminum smelting company (Redline et al. 1986). The particulates contained various metallic alloys: 61% of the particulates consisted of aluminum and other metals such as titanium, zinc, and nickel; 35% contained various aluminum silicates; 2% of the particles were silica. This finding confirms the possibility of titanium deposition in the lung tissue. Furthermore, since the worker had a case of pulmonary granulomatous disease, the identification of particulates lends support to the possible association between granulomatous lung disease and particle deposition. These results

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indicate that titanium can be deposited in the lungs of occupationally exposed workers, and that these deposits do not necessarily cause histopathological changes. It is also possible that in some cases these deposits do cause local pulmonary tissue irritation, which can progress to granulomatous lung disease. These results indicate that the severity of the pulmonary injury following exposure to titanium tetrachloride is related to the inhaled amount of the compound. It is also reasonable to assume that individuals with impaired respiratory function will be more susceptible to the effects of titanium tetrachloride.

The results of acute-, intermediate-, and chronic-duration exposure studies to titanium tetrachloride in animals support the observations made in humans. In female Sprague-Dawley rats, signs of pulmonary toxicity included wet noses, nasal discharge, swollen eyelids, and dyspnea following an acute inhalation exposure to titanium tetrachloride (Karlsson et al. 1986). These signs disappeared 48-72 hours after exposure, and lung histopathology 7 days later showed only minor lesions. Observations of respiratory effects were made in other acute-duration studies in rats (DuPont 1980), in intermediate-duration studies in rats (DuPont 1979), and in chronically exposed rats (EPA 1986; Lee et al. 1986). The findings from the DuPont (1979) study were used as the basis for derivation of an intermediate inhalation MRL. In the chronic study, the primary clinical finding was a concentration-related increase in the incidence of irregular respiration and abnormal lung noises in exposed animals. The major health effects of exposure to titanium tetrachloride were observed in the respiratory tract. The incidence of rhinitis increased with concentration and duration of exposure. Tracheitis also increased with duration and to a lesser degree with concentration. The 0.1 mg/m^3 in this study was considered a less serious LOAEL for adverse effects in the extrathoracic/tracheobronchial region. Gross pathology and histopathology showed compound-related changes in the lungs and thoracic lymph nodes in the form of foci laden with yellow titanium tetrachloride hydrolysis product. These foci were present on the lung pleural surface and on the slightly enlarged tracheobronchial lymph nodes. The pulmonary response also included the presence of the dust-laden macrophages, and the concentration-related hyperplasia of the alveolar lining. The findings of Lee et al. (1986) served as the basis for derivation of a chronic inhalation MRL.

Hematological Effects. No abnormal values for hemoglobin, white blood cells, neutrophils, monocytes, and basophils were found in 10 workers exposed for 4-17 years to low levels of titanium tetrachloride fumes (Lawson 1961). However, three of the workers had mild eosinophilia, and four had relative lymphocytosis. The significance of these effects is not known; there were no controls in

the study, and the observed lymphocytosis may have been caused by the influenza present among the workers at the time of the study.

The results from animal studies do not support the white blood cell observations made in humans. A significant increase in neutrophils ($p< 0.05$) and a decrease in lymphocytes were observed in Crl:CD rats after chronic inhalation exposure to titanium tetrachloride (EPA 1986; Lee et al. 1986). In addition, a significant decrease in erythrocytes and a significant increase in the mean cell volume and mean cell hemoglobin were observed in males after 18 months of exposure.

Dermal Effects. Titanium tetrachloride is a highly corrosive irritant to the skin, eyes, mucous membranes, and respiratory tract (EPA 1985b). Exposure to liquid titanium tetrachloride results in chemical and thermal skin injuries, unless appropriate treatment is used following the exposure (Lawson 1961). The corrosive thermal dermal injuries are not solely due to titanium tetrachloride, but result from the contact of titanium tetrachloride and water. This extremely vigorous reaction is exothermal, generating large quantities of heat. It also produces hydrochloric acid as one of the hydrolysis products which probably is responsible for the highly corrosive dermal effects. Therefore, the accidental exposure to titanium tetrachloride and its subsequent hydrolysis can result in the third-degree bums. The most severe bums in reported cases occurred in the areas that were occluded by either belts or shoes (Lawson 1961). These bums were deep, occasionally required skin grafting, and took a long time to heal. In all three cases the scars were surrounded by dark brown pigmentation. Although the reason for this scar coloration is not known, the authors felt it is possible that is represents accumulations of metallic titanium. Avoiding the initial use of water in the treatment following exposure to titanium tetrachloride is the single most important factor in preventing the hydrolysis that leads to thermal and chemical bums. Exposures causing dermal injuries of this extent are very unlikely to occur at the hazardous waste sites because of the excessive quantities of titanium tetrachloride needed to produce such corrosive effects.

Ocular Effects. Titanium tetrachloride is a highly corrosive irritant to the eyes (EPA 1985b). Four grades of eye bums were identified based on the description of eight cases of accidental occupational exposure (Chitkara and McNeela 1992). Grade I and grade II eye bums resolve without complications, while grade III and grade IV bums result in eye loss. Grade I eye injuries usually consist of mild defects of inferior comeal and conjunctival epithelium which heal within 2-3 days after the exposure. Grade II injuries affect the same eye structures, but are more severe and take longer to

heal. No information of grade III eye injuries was given. The grade IV eye injuries have corneal and conjunctival bums accompanied with conjunctival ischemia and lens opacity. Over a period of time (up to 2 months), this injury progressed to severe corneal stromal lysis and ultimately corneal perforation resulting in blindness. The exposures causing eye injuries of this extent are very unlikely to occur at the hazardous waste sites because of the high concentration of titanium tetrachloride needed to produce such corrosive effects and the instability of this chemical in the presence of moisture.

Immunological and Lymphoreticular Effects. Two studies reported lymphocytosis in humans following inhalation exposure to titanium tetrachloride. In one case, an elevated lymphocyte count was found in a worker after an accidental exposure to titanium tetrachloride (Park et al. 1984); in the other case, 4 of 10 workers chronically exposed to low levels of titanium tetrachloride fumes had relative lymphocytosis (Lawson 1961). However, it is difficult to interpret these findings because no controls were available, and there was influenza among the workers at the time the study was conducted. The results of *in vitro* evaluation of the immune status of an exposed worker was also inconclusive. Impaired cellular immune function was found in a 45year-old man who had decreased responses to selected mitogens (phytohemagglutinin, pokeweed mitogen, and concanavalin A) commonly used for the assessment of immune status (Redline et al. 1986). It was also not possible to determine if prolonged exposure to titanium tetrachloride could cause sensitization of the delayed hypersensitivity type because the response was positive in only 2 of 4 tests performed over an 1 l-month period. The relevance of these results to humans living near waste sites is unknown.

The studies in animals indicate that dust-laden macrophage infiltration of the lung and adjacent lymph nodes is the prevalent immunological response observed following chronic inhalation exposure to titanium tetrachloride (EPA 1986; Lee et al. 1986). The results indicate the beginning of an active cell-mediated immune response in the exposed animals due to the accumulation of titanium tetrachloride hydrolysis products. These data are insufficient to determine if individuals exposed to low levels of titanium tetrachloride at hazardous waste sites (unlikely due to instability of titanium tetrachloride) would develop an active cell-mediated immune response to titanium tetrachloride.

Neurological Effects. No studies were located regarding neurological effects in humans following exposure to titanium tetrachloride by any route. Limited information was provided in a single inhalation study in which no histopathological alterations were observed in the brains of rats exposed intermittently to up to 40 mg/m^3 titanium tetrachloride for 4 weeks (DuPont 1979); no further

neurological end points were evaluated in that study. The relevance of this finding to human health is unknown.

Reproductive Effects. No information was located regarding reproductive effects in humans after inhalation exposure to titanium tetrachloride by any route. Only one study was located that provided information regarding reproductive effects in animals. That study (DuPont 1979) reported that no histopathological alterations were observed in the testes and epididymis from rats exposed intermittently to up to 40 mg/m^3 titanium tetrachloride for 4 weeks; female rats were not tested. Since neither reproductive function nor other reproductive end points were assessed in the DuPont (1979) study, the relevance of these limited results to human health cannot be ascertained.

Developmental Effects. No studies were located regarding developmental effects of titanium tetrachloride in humans or animals after inhalation, oral, or dermal exposure. However, a study was located which examined neurodevelopmental parameters in offspring of rats administered titanium tetrachloride intraperitoneally during gestation (Tsujii and Hoshishima 1979). The results showed that several reflex responses were altered (either delayed or accelerated). However, because the authors did not conduct a statistical analysis of the results, the significance of the findings is questionable. Furthermore, because the route of administration was by injection, the relevance to potential exposure by humans is unknown.

Genotoxic Effects. No studies investigating the potential of titanium tetrachloride to induce genetic damage in humans or whole animals were found. As the data presented in Table 2-2 indicate, the in *vitro* testing of titanium tetrachloride for adverse effects on genetic material has been limited to several bacterial strains. However, titanium tetrachloride rapidly hydrolyses in aqueous environments; consequently, results from *in vivo* or *in vitro* testing in aqueous media must be interpreted with caution. In the available studies, titanium tetrachloride, at unspecified doses, was not mutagenic in *Salmonella typhimurium* strains TA1537, TA2637, TA98, Tal00, or TA102; exogenous metabolic activation was not included in the assay (Ogawa et al. 1987). The same investigators did not observe an enhancement of mutagenesis when *S. typhimurium* strains TA1537 or TA2637 were exposed simultaneously to titanium tetrachloride doses ranging from 1 to 10,000 μmol/plate and 100 μmol/plate 9-aminoacridine (9-AA). The well-known mutagen 9-AA was included in the experiment because the findings from earlier studies conducted by these investigators suggested that 9-AA may serve as a

Table 2-2. Genotoxicity of Titanium Tetrachloride *In Vitro*

Species (test system)	End point	Results		References
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium (TA1537, TA2637, TA98, TA100)	Gene mutation	NT	–	Ogawa et al. 1987
S. typhimurium (TA1537, TA2637)	Gene mutation	NT	–[a]	Ogawa et al. 1987
Bacillus subtilis (H17, M45)	DNA damage	NT	–	Kada et al. 1980; Kanematsu et al. 1980

[a]Bacterial strains were simultaneously exposed to titanium tetrachloride and 9-aminoacridine.

– = negative results, DNA = deoxyribonucleic acid; NT = not tested

carrier of metal cations across cellular membranes. Titanium tetrachloride was determined to be toxic

to the bacteria since, even after washing to remove the chemical, no revertant colonies grew.

Nonactivated doses of titanium tetrachloride ranging from 0.005 to 0.5 molal did not cause preferential

inhibition of recombination repair-deficient (rec⁻) *Bacillus subtilis* strain M45 as compared to

deoxyribonucleic acid (DNA) repair-proficient (rec⁺) strain H17 (Kanematsu et al. 1980). Similarly,

unspecified concentrations of titanium tetrachloride in the absence of metabolic activation were

reported to be negative in the *B. subtilis* ret ⁺/⁻ assay (Kada et al. 1980).

Because titanium tetrachloride rapidly hydrolyzes upon contact with water, the findings from the

limited microbial assay are insufficient to reach any conclusions regarding the potential, if any, of

titanium tetrachloride to induce genotoxic effects.

Cancer. Epidemiological studies are inadequate to determine if titanium tetrachloride causes cancer

in occupationally exposed individuals. However, statistical analysis of the available mortality and lung

cancer incidence data indicate that there is no association between titanium tetrachloride exposure and

lung cancer mortality (EPA 1990b; Fayerweather et al. 1992).

Lesions characterized as lung squamous cell carcinoma and keratinizing squamous cell carcinoma were

observed in rats chronically exposed to titanium tetrachloride (EPA 1984, 1986; Lee et al. 1986).

Following chronic inhalation exposure of rats, these lesions occurred in the alveoli with squamous

metaplasia and next to the alveolar ducts with aggregated dust-laden macrophages; the lesions were

probably a result of chronic tissue irritation from dust-laden macrophages and cellular debris. No

metastases were found in any of the rats. According to the study authors, these lesions are a unique

type of experimentally induced tumors that is not usually seen in humans or other animals. Their

etiology is also different from human squamous cell carcinomas. Human lung squamous cell

carcinomas arise in the basal cells of the bronchial epithelium, while cystic keratinizing squamous cell

carcinomas observed in this study developed from the alveolar lining cells that are close to the alveolar

duct region. Recent information provided by DuPont (1994) indicate that after reexamination of the

tumor data of Lee et al. (1986), a group of pathologists agreed that the lesions should be rediagnosed

as either squamous metaplasia or proliferative keratin cysts, and that based on the reevaluation of the

evidence, titanium tetrachloride was not carcinogenic in rats.

2. HEALTH EFFECTS

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They
have been classified as markers of exposure, markers of effect, and markers of susceptibility
(NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of
biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is
a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent
and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC
1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific
metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the
use and interpretation of biomarkers of exposure. The body burden of a substance may be the result
of exposures from more than one source. The substance being measured may be a metabolite of
another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several
different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life)
and environmental conditions (e.g., duration and route of exposure), the substance and all of its
metabolites may have left the body by the time samples can be taken. It may be difficult to identify
individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g.,
essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to titanium
tetrachloride are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within
an organism that, depending on magnitude, can be recognized as an established or potential health
impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals
of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital
epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or
decreased lung capacity. Note that these markers are not often substance specific. They also may not
be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of
effects caused by titanium tetrachloride are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's
ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an

intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Titanium Tetrachloride

Because of the chemical characteristics of titanium tetrachloride, namely its very rapid hydrolysis in the presence of small amounts of water, it is unlikely that it would exist in the blood. Also, no methods for the measurement of titanium tetrachloride in biological samples were located. Although very little information is available, some of the titanium tetrachloride hydrolysis products could be used as biomarkers to identify or possibly to quantify the exposure to titanium tetrachloride. One of the more stable hydrolysis products of titanium tetrachloride is titanium dioxide. The use of electron microscopy and/or spectrometric and spectrographic analysis using X-ray fluorescence showed the presence of carbon-like, birefractive, pigment aggregations under the pleura that consisted of O.l-0.4μm-diameter black particles very similar to titanium dioxide in the lysosomes of alveolar and lymph node macrophages of three titanium dioxide processing factory workers (Elo et al. 1972). Following accidental exposure to titanium tetrachloride, scars formed after second- or third-degree burns were surrounded by dark pigmentation (Lawson 1961). The bums were the result of the vigorous interaction of titanium tetrachloride and water, which was used following the exposure. Although the nature of this dark pigmentation is not known, the authors of the study felt it is possible that it is due to the presence of titanium dioxide deposits. These observations suggest that titanium dioxide could be used as biomarker of titanium tetrachloride exposure.

Another useful indication of dermal exposure to titanium tetrachloride is low pH of the skin (Lawson 1961). This low skin pH results from the presence of hydrochloric acid, which is one of the titanium tetrachloride hydrolysis products. The low pH may indicate that additional decontamination is needed to prevent the acid bums.

2.6.2 Biomarkers Used to Characterize Effects Caused by Titanium Tetrachloride

For more information on biomarkers for renal and hepatic effects of chemicals see *ATSDRKDC Subcommittee Report on Biological Indicators of Organ Damage* (1990) and for information on biomarkers for neurological effects see OTA (1990).

2. HEALTH EFFECTS

No description of biomarkers that could be used to characterize the effects caused by exposure to titanium tetrachloride was found in the course of the literature search.

2.7 INTERACTIONS WITH OTHER CHEMICALS

Limited information is available regarding the influence of substances other than water on the toxicity of titanium tetrachloride. Titanium tetrachloride interacts vigorously with water in an exothermic reaction that produces heat and hydrochloric acid. Under those circumstances, exposure to titanium tetrachloride can result in a severe thermal and chemical injury.

Acute exposure of Sprague-Dawley rats and Syrian hamsters to the reactant products of aerosolized titanium tetrachloride and ammonium hydroxide did not cause any significant changes in either species (DOE 1978). The status of the animals was evaluated 1 hour after exposure or 30 days after exposure. The mixture of the two chemicals was used to generate cold smoke, which is produced by the reaction of titanium tetrachloride with concentrated ammonium hydroxide; the resulting products are titanium dioxide and ammonium chloride (Smith et al. 1980).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to titanium tetrachloride than will most persons exposed to the same level of titanium tetrachloride in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of titanium tetrachloride, or compromised function of target organs affected by titanium tetrachloride. Populations who are at greater risk due to their unusually high exposure to titanium tetrachloride are discussed in Section 5.6, Populations With Potentially High Exposure.

Persons with bronchitis, pneumoconiosis, bronchial asthma, pulmonary tuberculosis, and diseases of the upper respiratory tract are at risk because of the toxic nature of titanium tetrachloride fumes (Mezentseva et al. 1963). For the same reason, work with titanium tetrachloride is contraindicated in persons with pulmonary or cardiovascular conditions that make it difficult for them to wear a protective mask (Mezentseva et al. 1963).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to titanium tetrachloride. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to titanium tetrachloride. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

In cases of acute dermal exposure to liquid titanium tetrachloride, immediate rinsing with water should not be used as a treatment (HSDB 1995). Rather, dry wiping of the skin with towels or cotton gauze is recommended as the best first action to minimize the effects of exposure. After dry wiping, a light-yellow-to-white granular deposit may still remain on the skin surface (HSDB 1995). At this stage, copious amounts of cool water should be used to completely decontaminate the exposed skin. A similar procedure is recommended in case of eye exposure, wipe the eye area and immediately rinse the eye with water; neutralizing solutions such as sodium bicarbonate should be avoided (HSDB 1995). Wearing protective clothing and goggles is recommended as a preventative measure (Chitkara and McNeela 1992). In cases of inhalation exposure, it is recommended that the patient be moved to fresh air and be monitored for respiratory distress (HSDB 1995). Since inhalation is the most probable route of exposure, early prophylactic treatment may include oxygen to prevent possible pulmonary complications (HSDB 1995). Accidental ingestion of titanium tetrachloride should be followed by dilution with milk and water (HSDB 1995). Neither the administration of bicarbonate to neutralize nor the induction of vomiting is recommended. Activated charcoal as a means to prevent absorption seems to be of no value (HSDB 1995). Although corticosteroid therapy improved the pulmonary status in one patient (Park et al. 1984), and prednisone can be used at l-2 mg/kg/day, the benefits of the use of steroids are debatable (HSDB 1995).

2.9.2 Reducing Body Burden

No information was located regarding reduction of body burden following exposure to titanium tetrachloride by any route.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The toxicity of titanium tetrachloride stems from its vigorous hydrolysis in the presence of water. This reaction generates heat and hydrochloric acid (Chitkara and McNeela 1992; Lawson 1961). To interfere successfully with the possible mechanism of titanium tetrachloride toxicity, the chemical and thermal injury that follows exposure in the presence of water should be prevented. That is done by wiping of the exposed site with a dry cloth as thoroughly as possible and avoiding the initial rinsing with water at all costs. One study suggests topical steroids and ascorbate, antibiotics, and mydratics, as well as oral ascorbate in cases of very severe injuries (Chitkara and McNeela 1992).

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of titanium tetrachloride is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of titanium tetrachloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Titanium Tetrachloride

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to titanium tetrachloride are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of titanium tetrachloride. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Projiles*

Figure 2-2. Existing Information on Health Effects of Titanium Tetrachloride

Human

Animal
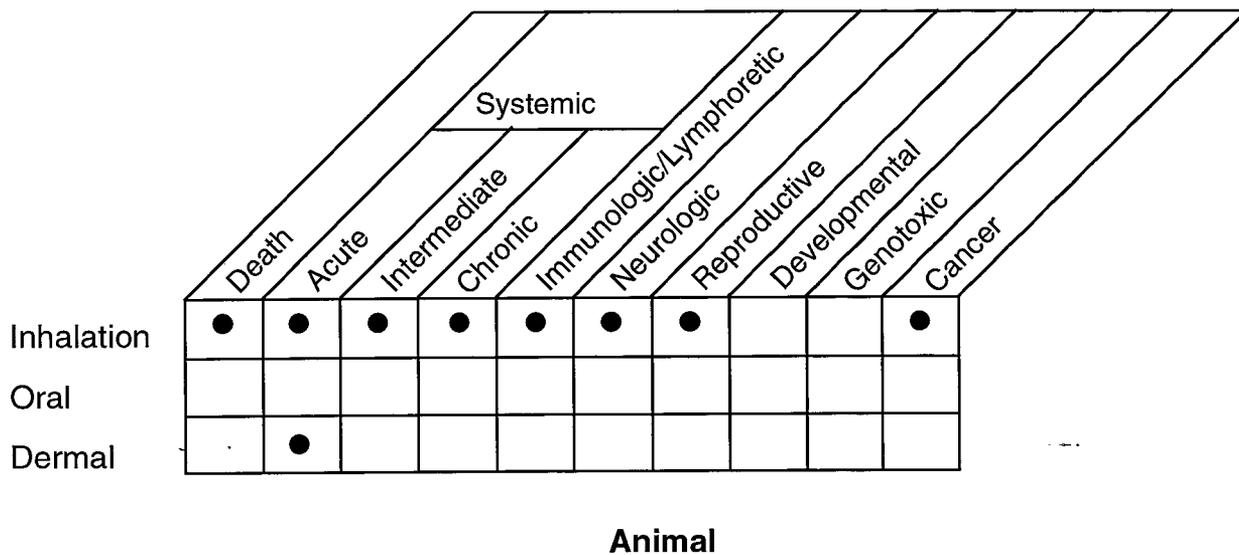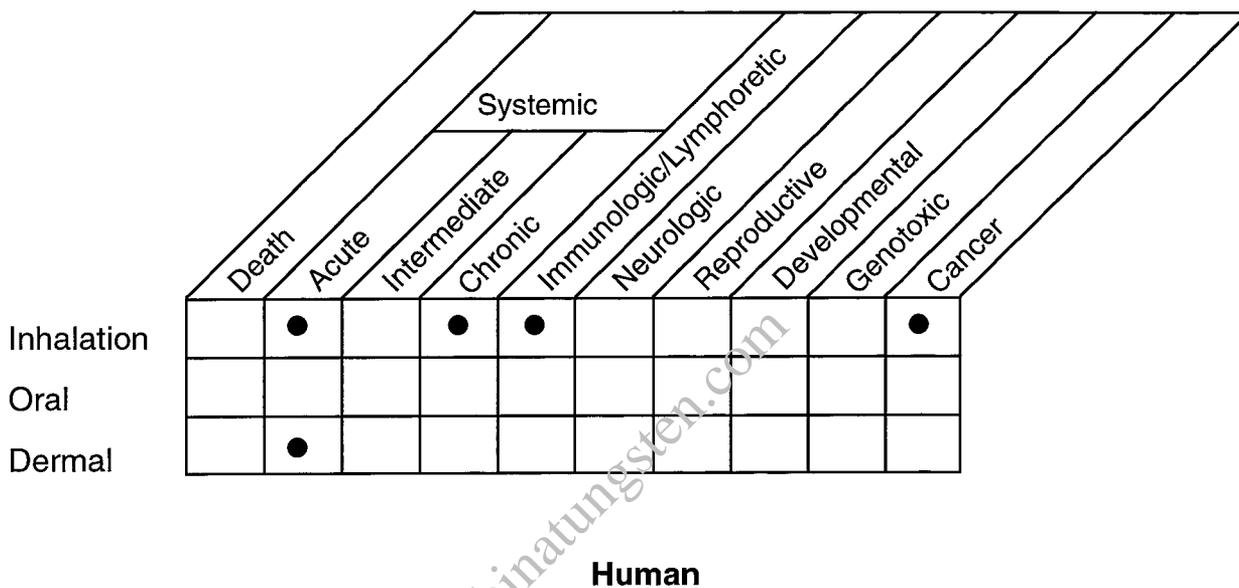
●   Existing Studies

(ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The vast majority of literature reviewed regarding the health effects of titanium tetrachloride in humans concerned case reports and chronic-duration epidemiological studies of workers employed in industries using titanium tetrachloride and case reports of accidental exposure of workers to titanium tetrachloride. For workers employed in industries using titanium tetrachloride, the major route of exposure is by inhalation of the hydrolyzed aerosol. In cases of accidental spills, the predominant route of exposure is also inhalation unless there is extensive dermal contact. Therefore, the information on acute-duration exposure comes from inhalation and dermal exposure data, and information on chronic-duration exposure comes almost exclusively from inhalation exposure data. The occupational exposure data are often limited by exposures to other chemicals, by the lack of information on the dose, and by lack of detail on the duration of exposure. No information is available regarding neurological, developmental, or reproductive effects in humans after exposure by any route, and no information is available regarding any effects in humans following oral exposure.

All of the information regarding health effects of titanium tetrachloride in animals was obtained from studies in which the exposure to titanium tetrachloride occurred by the inhalation route. There is almost no information concerning health effects in animals following oral or dermal exposures.

Because titanium tetrachloride rapidly hydrolyzes in the presence of water and will not survive in the environment, the major potential route of exposure is inhalation for persons involved in industries utilizing titanium tetrachloride. In the case of accidental spills that may occur in the manufacturing process, exposure is more likely to be exposed via the dermal route. Therefore, additional information on health effects via these two routes would be of value.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. Acute-duration inhalation exposure data in humans indicate that the lungs are the major target organ of titanium tetrachloride toxicity. Symptoms of pulmonary toxicity range from mild such as ticklish cough and tightness in the chest (Ross 1985) to more severe such as shallow breathing, upper airway stridor progressing to hypoxia, and formation of pulmonary infiltrates

that are characteristic of respiratory distress syndrome (Park et al. 1984). Lymphocytosis was reported in several cases of accidental inhalation exposure, but the results are not sufficient to conclude that they were a consequence of the exposure (Lawson 1961; Park et al. 1984). The data in animals support the observations made in humans regarding respiratory injury following acute inhalation exposure to titanium tetrachloride; irritation, wet nose, nasal discharge, and dyspnea were observed in rats following a 10-minute inhalation exposure to titanium tetrachloride (Karlsson et al. 1986). Exposure to lethal concentrations induced severe histopathologic alterations in the respiratory epithelium, corneal opacity and conjunctivitis, and weight loss in rats (DuPont 1980). Insufficient information was available to calculate an acute-duration inhalation MRL for titanium tetrachloride. Additional studies on the acute exposure to titanium tetrachloride in animals are needed to examine the histopathologic effects in various regions of the respiratory system.

No information was available regarding acute-duration oral exposure of titanium tetrachloride in either humans or animals. This is not expected to be a major route of exposure to titanium tetrachloride because of its rapid hydrolysis in moist air.

The skin and the eyes are target organs following acute dermal exposure to titanium tetrachloride (Chitkara and McNeela 1992; Lawson 1961; Ross 1985). Results from these studies indicate that the eyes may be the most sensitive target organ for the effects of brief dermal exposure to titanium tetrachloride. The injury to the eye depends on the degree of the burn (caused by exothermal hydrolysis reaction of titanium tetrachloride an hydrochloric acid) and of the treatment that follows the exposure. Further studies examining the effects of acute dermal exposure to titanium tetrachloride in animals seem unnecessary at this time.

Intermediate-Duration Exposure. No information is available regarding effects of intermediate-duration exposure to titanium tetrachloride in humans. Reports of the effects of intermediate-duration inhalation exposure in rats (DuPont 1979; EPA 1986; Lee et al. 1986) describe effects such as nasal irritation and lung abnormalities that are almost identical to those observed following chronic exposure (see Chronic-Duration Exposure and Cancer, below). An intermediate inhalation MRL was derived based on the results of DuPont (1979). Given the similar findings following intermediate- and chronic-duration exposure, additional intermediate-duration inhalation studies are not necessary at this time.

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No information was available regarding intermediate-duration oral or dermal exposure of titanium tetrachloride in either humans or animals. However, additional studies are probably not warranted because of the corrosive nature of the compound and because effects are most likely to be localized.

Chronic-Duration Exposure and Cancer. Two epidemiological studies were conducted on workers who were chronically exposed to titanium tetrachloride. Doses were not well defined, concomitant inhalation and possible dermal exposures occurred, and there may have been exposure to other chemicals. It may be possible to recommend a population from DuPont that has been already studied for future investigation of effects caused by chronic exposures since they do have the records of all of their employees potentially exposed to titanium tetrachloride. Data from the existing epidemiological studies indicate that the pulmonary system is the main target for chronic inhalation exposure in humans. Further studies on the causes of the pulmonary abnormalities seen in some workers with chronic exposure to titanium tetrachloride may be useful in determining long-term lung damage that may be indicative of exposure to the chemical (Garabrant et al. 1987). Similarly, chronic inhalation exposure in animals also indicates that lungs are the primary target organ for chronic toxicity in rats (EPA 1986; Lee et al. 1986). A chronic inhalation MRL was derived based on the results of Lee et al. (1986). No studies on chronic oral exposure in humans or animals were located.

Epidemiological studies that examine the incidence of cancer in workers exposed to titanium tetrachloride did not show that this compound is carcinogenic in humans. These studies are limited by lack of data on dose and precise duration of exposure (EPA 1990b; Fayerweather et al. 1992). Although lung squamous cell carcinoma and keratinizing squamous cell carcinoma were diagnosed in rats after chronic inhalation exposure to titanium tetrachloride (EPA 1984, 1986; Lee et al. 1986), recent data suggest that the lesions are most likely not neoplastic (DuPont 1994). Furthermore, it is difficult to estimate their relevance to lung tumors in humans because they have a different etiology and cell type (EPA 1984, 1986; Lee et al. 1986). Additional studies in a species other than the rat by the inhalation route would help clarify the carcinogenic potential of titanium tetrachloride. These studies would also elucidate the possibility that the accumulation of titanium metallic particles in the lungs may cause a sufficient degree of irritation to lead to cancer formation or lung granulomatous disease.

Genotoxicity. No conclusions can be reached regarding the potential, if any, of titanium tetrachloride to induce genetic damage. It is probable that valid results cannot be obtained in any

in vivo or *in vitro* test systems because of the rapid hydrolysis of titanium tetrachloride in aqueous environments.

Reproductive Toxicity. No information was located regarding reproductive toxicity in humans following exposure to titanium tetrachloride. A single 4-week inhalation study in rats provided very limited information (DuPont 1979). Studies examining the reproductive effects of titanium tetrachloride would help determine if toxic effects would occur as a result of acute- or chronic-duration inhalation or dermal exposure to titanium tetrachloride.

Developmental Toxicity. No information was located regarding developmental toxicity in humans or animals following exposure to titanium tetrachloride by the inhalation, oral, or dermal route. One study was located that examined neurodevelopmental effects of titanium tetrachloride on offspring from rats administered the chemical intraperitoneally during gestation (Tsujii and Hoshishima 1979). Studies examining the developmental effects of titanium tetrachloride would help determine if toxic effects would occur as a result of acute- or chronic-duration inhalation or dermal exposure to titanium tetrachloride.

Immunotoxicity. Isolated cases of titanium tetrachloride-induced lymphocytosis have been reported in humans exposed by the inhalation route (Lawson 1961; Park et al. 1984). The interpretation of these results is limited because no details of the exposure were provided (Park et al. 1984), no controls were provided, and an epidemic of influenza was concurrent (Lawson 1961). Impaired cellular immune function evident in reduced mitogen responsiveness was present in a worker exposed chronically to titanium metal (Redline et al. 1986). In two out of four assays done with PBLs from this worker, the response to titanium tetrachloride was positive, indicating the possible sensitization against titanium tetrachloride. More information is needed to confirm this finding and determine if there is a relationship between the delayed hypersensitivity observed in this worker and the accumulation of metallic titanium in the pulmonary granuloma also found in this case. Additional studies of dermal and inhalation exposure examining the potential effects of the longer Exposure in animals would help elucidate the immunotoxicity of titanium tetrachloride.

Neurotoxicity. No information was located regarding neurotoxicity in humans following exposure to titanium tetrachloride. Data in animals were restricted to a limited-scope single 4-week inhalation study in rats (DuPont 1979). However, studies on the neurotoxicity of this compound are probably not

warranted because of the corrosive nature of the compound and because effects are most likely to be localized.

Epidemiological and Human Dosimetry Studies. Human studies on titanium tetrachloride consist of either case reports of accidental occupational exposure or epidemiological studies of workers employed in the manufacture of metallic titanium, titanium salts, titanium pigments, or mordant dyes. Because of the rapid hydrolysis of titanium tetrachloride in the presence of small amounts of water, the exposures in case reports and epidemiological studies are virtually all by the inhalation route, with two accidental exposures via the dermal route with subsequent inhalation. A good database of occupationally exposed workers (EPA 1990b; Fayerweather et al. 1992) exists at DuPont and was used to evaluate the association between the exposure to titanium tetrachloride and lung cancer incidence and mortality. Locating populations for future epidemiological studies may be difficult if exposure records of potentially exposed workers are not maintained. Since titanium tetrachloride is used to generate smoke screens, the records of potentially exposed individuals may be available from the military. If such groups of exposed individuals are located, investigation regarding systemic, immunological, neurological, developmental, and reproductive effects, and correlation of these effects with the exposure levels of titanium tetrachloride would provide useful information. Further studies on occupationally exposed workers may be useful in determining chronic effects of this compound.

Because of its rapid hydrolysis, very few persons are likely to be exposed to titanium tetrachloride at hazardous waste sites.

Biomarkers of Exposure and Effect.

Exposure. It is not possible to determine the levels of titanium tetrachloride in the blood because titanium tetrachloride is very rapidly hydrolyzed in the presence of small amounts of water. However, some titanium tetrachloride hydrolysis products could be used as biomarkers to identify or possibly quantify the exposure to titanium tetrachloride. One of the more stable hydrolysis products of titanium tetrachloride is titanium dioxide. The use of electron microscopy, and spectrometric and spectrographic analysis using X-ray fluorescence, showed the presence of carbon-like particles that were very similar to titanium dioxide in the lysosomes of alveolar and lymph node macrophages of three titanium dioxide processing factory workers (Elo et al. 1972). Also present in the lung and

lymph node tissue samples were large quantities of titanium (presumably titanium dioxide). Further studies would be useful.

Effect. Following accidental occupational exposure to titanium tetrachloride, the scars left from the second- or third-degree bums were surrounded by dark pigmentation (Lawson 1961). Although the nature of this dark pigmentation is not known, the authors of the study suggested it may be due to the presence of metallic titanium deposits. These observations suggest that both titanium dioxide and metallic titanium might be used as a biomarkers of titanium tetrachloride exposure.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding absorption, distribution, metabolism, or excretion of titanium tetrachloride; however, further studies are not warranted because of the very reactive nature of this compound.

Comparative Toxicokinetics. No studies were located regarding toxicokinetics in any animal species; however, further studies are not warranted for titanium tetrachloride because of the very reactive nature of this compound.

Methods for Reducing Toxic Effects. The most important way to prevent toxic effects of titanium tetrachloride in the occupational setting is to use protective clothing and a respirator. If exposure occurs, the use of water for decontamination is dangerous. To prevent thermal and chemical injuries that result from the vigorous hydrolysis of titanium tetrachloride, wiping with dry towels or cotton gauze is recommended to minimize the effects of exposure. After dermal exposure and dry wiping, a light-yellow-to-white granular deposit may remain on the skin surface (HSDB 1995). At this stage, copious amounts of cool water should be used to decontaminate the exposed skin completely. Since inhalation is the most probable route of exposure, early prophylactic treatment may include oxygen to prevent possible pulmonary complications. Further exposure should, of course, be avoided (HSDB 1995). Although corticosteroid therapy improved the pulmonary status in one patient (Park et al. 1984), and prednisone can be used at l-2 mg/kg/day, the use of steroids is debatable (HSDB 1995). One study suggested the use of topical steroids and ascorbate, the use of antibiotics and mydratics, and the use of oral ascorbate in cases of very severe injuries (Chitkara and McNeela 1992).

2.10.3 Ongoing Studies

No ongoing studies regarding the health effects of titanium tetrachloride were reported in the Federal Research in Progress File database (FEDRIP 1995).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of titanium tetrachloride is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of titanium tetrachloride is located in Table 3-2.

Table 3-1. Chemical Identity of Titanium Tetrachloride

Characteristic	Information	Reference
Chemical name	Titanium tetrachloride	HSDB 1995
Synonym(s)	Tetrachlorotitanium, titanic chloride, titanium chloride, others	HSDB 1995
Registered trade name(s)	No data	
Chemical formula	$TiCl_4$	HSDB 1995
Chemical structure		OHM/TADS 1992

$$Cl-Ti-Cl$$

with Cl above and Cl below the Ti
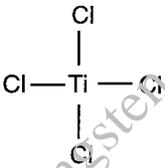
Identification numbers:		
CAS registry	7550-45-0	HSDB 1995
NIOSH RTECS	XR1925000	HSDB 1995
EPA hazardous waste	No data	HSDB 1995
OHM/TADS	7217310	HSDB 1995
DOT/UN/NA/IMCO shipping	IMCO/UN: #8.0/1838; DOT: #1838	CHRIS 1985
HSDB	870	HSDB 1995
NCI	No data	

CAS = Chemical Abstracts Service; CHRIS = Chemical Hazards Response Information System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Titanium Tetrachloride

Property	Information	Reference
Molecular weight	189.70	Sax and Lewis 1989
Color	Colorless	Merck 1989
Physical state	Liquid	CHRIS 1985
Melting point	−24.1 °C	Merck 1989
	−24 °C	NFPA 1994
Boiling point	136.4 °C	Merck 1989
Density:		
at 20 °C	1.726 g/cm^3	Merck 1989
Odor	Penetrating acid odor	Merck 1989
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20 °C	Soluble in cold water	Merck 1989
	Reacts	NFPA 1994
Organic solvent(s)	Soluble in alcohol	Merck 1989
Partition coefficients:		
Log K_{ow}	No data	
Log K_{oc}	No data	
Vapor pressure		
at 20 °C	10.0 mm Hg	Whitehead 1983
at 22 °C	9.6 mm Hg	NFPA 1994
Henry's law constant:		
at 20 °C	No data	
at 30 °C	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	Nonflammable	OHM/TADS 1992
Conversion factors	1 mg/m^3 = 7.76 ppm[a]	Calculated
	1 ppm = 0.129 mg/m^3	Calculated
Explosive limits	Reactive only under extreme conditions	OHM/TADS 1992

[a]1 mg/m^3 = 1 ppm × 189.70/24.45

CHRIS = Chemical Hazards Response Information System; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; NFPA = National Fire Protection Association

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Titanium tetrachloride is a colorless-to-light-yellow watery liquid that is produced by the chlorination of titanium compounds by a continuous process in a fluid-bed reactor. Minerals with a high titanium content, such as beneficiated ilmenite, mineral r-utile, and leucoxene, are used in the production of titanium tetrachloride. Carbon (usually as coke) is also added during the chlorination process as a reducing agent because the titanium compounds contain oxygen (Whitehead 1983).

The estimated production of titanium tetrachloride in the United States in 1972 was at least 5,670,000,000 grams (12,474,000 pounds) (HSDB 1995); in 1975, it was at least 9,500,000,000 grams (20,900,000 pounds) (HSDB 1995); and in 1980, it was 2,500,000 tons (5,000,000,000 pounds) (Whitehead 1983). More recently, the aggregate production volume for titanium tetrachloride reported in the Toxic Substances Control Act Inventory for 1990 was 3,150,556,000 pounds (1,575,278 tons) (CICIS 1993).

A list of titanium tetrachloride production and processing facilities in the United States along with the production or processing volume for each facility are provided in Table 4-l (TR193 1995).
Table 4-l lists the facilities in each state that manufacture or process titanium tetrachloride, the intended use, and the range of maximum amounts of titanium tetrachloride that are stored on site. The data listed in Table 4-l are derived from the Toxics Release Inventory (TR193 1995). The TRI data should be used with caution since only certain types of facilities are required to report. Therefore, this is not an exhaustive list.

4.2 IMPORT/EXPORT

No information on import or export volumes for titanium tetrachloride was located.

4.3 USE

Titanium tetrachloride is used as an intermediate in the manufacture of titanium metal, titanium dioxide, titanous chloride pigments, iridescent glass, artificial pearls, and as a starting material for a

Table 4-1. Facilities That Manufacture or Process Titanium Tetrachloride

Facility	Location[a]	Range of maximum amounts on-site in pounds	Activities and uses
DU PONT	AXIS, AL	100,000-999,999	As a reactant
DU PONT	ANTIOCH, CA	100,000-999,999	Produce; For on-site use/processing; As a reactant
PFIZER INC.	CT	10,000-99,999	As a reactant; As a chemical processing aid
DU PONT	EDGEMOOR, DE	1,000,000-9,999,999	Produce; For on-site use/processing; For sale/distribution; As a reactant
KEMIRA INC.	SAVANNAH, GA	1,000,000-9,999,999	Produce; For on-site use/processing; For sale/distribution; As a reactant
AMERICAN SYNTHETIC RUBBER	LOUISVILLE, KY	10,000-99,999	As a chemical processing aid
LOUISIANA PIGMENT CO. L.P.	WESTLAKE, LA	100,000-999,999	Produce; For on-site use/processing; As a reactant
HIMONT USA INC.	LAKE CHARLES, LA	100,000-999,999	As a reactant
SHELL NORCO MFG. COMPLEX	NORCO, LA	100,000-999,999	As a reactant
SCM CHEMICALS	BALTIMORE, MD	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
AKZO CHEMICALS INC.	WESTON, MI	10,000-99,999	In repackaging
ANDERSON DEVELOPMENT CO.	ADRIAN, MI	10,000-99,999	As a reactant
DU PONT DELISLE	PASS CHRISTIAN, MS	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
KERR-MCGEE CHEMICAL CORP.	HAMILTON, MS	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
HUNTSMAN POLYPROPYLENE CORP.	WEST DEPTFORD TWP., NJ	10,000-99,999	As a chemical processing aid
AKZO NOBEL CHEMICALS INC.	EDISON, NJ	100,000-999,999	As a reactant
E. I. DU PONT DE NEMOURS & CO.	NJ	100,000-999,999	As a reactant
TITANIUM METALS CORP.	HENDERSON, NV	1,000,000-9,999,999	Produce; For on-site use/processing; For sale/distribution; As a reactant
TAM CERAMICS INC.	NIAGARA FALLS, NY	10,000-99,999	As a reactant
CORNING INC.	NY	10,000-99,999	As a reactant
SCM CHEMICALS	ASHTABULA, OH	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
SCM CHEMICALS AMERICAS	ASHTABULA, OH	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant

Table 4-1. Facilities That Manufacture or Process Titanium Tetrachloride (continued)

Facility	Location[a]	Range of maximum amounts on-site in pounds	Activities and uses
PHILLIPS RESEARCH CENTER	BARTLESVILLE, OK	10,000-99,999	As a reactant; Ancillary uses
OREGON METALLURGICAL CORP.	ALBANY, OR	1,000,000-9,999,999	As a reactant
PFIZER INC.	PR	10,000-99,999	As a reactant
DU PONT	NEW JOHNSONVILLE, TN	1,000,000-9,999,999	Produce; For on-site use/processing; As a reactant
AMOCO CORP.	TX	10,000-99,999	As a chemical processing aid
SOLVAY AMERICA INC.	TX	10,000-99,999	As a chemical processing aid
CATALYST RESOURCES	PASADENA, TX	10,000-99,999	As a reactant
ETHYL CORP.	PASADENA, TX	10,000-99,999	As a chemical processing aid
CHEVRON CORP.	TX	10,000-99,999	As a chemical processing aid
NA	TX	10,000-99,999	As a reactant
TEXAS EASTMAN DIV.	LONGVIEW, TX	10,000-99,999	As a reactant; Ancillary uses
GOODYEAR TIRE & RUBBER CO.	CHEEK, TX	10,000-99,999	As a chemical processing aid
OCCIDENTAL CHEMICAL CORP.	WADSWORTH, TX	10,000-99,999	As a chemical processing aid
OCCIDENTAL PETROLEUM CORP.	TX	10,000-99,999	As a chemical processing aid
E. I. DU PONT DE NEMOURS & CO.	TX	10,000-99,999	As a chemical processing aid
AKZO NOBEL CHEMICALS INC.	GALLIPOLIS FERRY, WV	10,000-99,999	As a chemical processing aid

Source: TRI93 1995

[a] Post office state abbreviation used

variety of organic and inorganic titanium compounds. It is also used as a mordant dye, a polymerization catalyst, and as a catalyst in many organic syntheses in the chemical industry (Chitkara and McNeela 1992; EPA 1985b; Merck 1989; Nordman and Berlin 1986; OHM/TADS 1992; Stokinger 1981; Whitehead 1983).

Titanium tetrachloride was formerly used with potassium bitartrate as a mordant in the textile industry, with dyewoods to dye leather, and as a smoke-producing screen with ammonia for the military (Merck 1989; Whitehead 1983).

4.4 DISPOSAL

The recommended disposal methods for titanium tetrachloride (including its container) include disposal in a landfill or by incineration (IRPTC 1985; OHM/TADS 1992). Small spills or leaks of titanium tetrachloride should be covered with a sufficient amount of sodium bicarbonate. The mixture should be removed and placed in an appropriate container such as a fiber drum, plastic bag, or carton, and then incinerated (IT11 1984; OHM/TADS 1992). Alternatively, titanium tetrachloride spills may be spread in a thin layer on the ground and dispersed by large amounts of water into a sewer. Spill areas should be washed thoroughly. The local waste water treatment authority should be notified of any discharge (IT11 1984).

No additional information on disposal methods for titanium tetrachloride was located.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Titanium tetrachloride is an inorganic compound that undergoes rapid hydrolysis upon contact with water. On contact with moist air, it produces a heavy, dense white smoke composed of fine particles of hydrochloric acid, titanium oxychloride, and titanium dioxide. It may be released to air during production and/or use, or as a result of chemical spills. Because it hydrolyzes upon contact with water, it is unlikely to be transported significant distances in any environmental media. However, one of its hydrolysis products, titanium dioxide, may persist in soils or sediments. The other hydrolysis product, hydrochloric acid, dissociates in water and air.

Exposure to titanium tetrachloride is primarily occupational, with titanium industry workers having the greatest potential exposure. Exposure to fumes and vapors can occur during handling of titanium tetrachloride and may also occur in the chlorinating department during production of titanium dioxide. Exposure can also occur by the dermal route, particularly in cases of occupational spills. Members of the general population are not likely to receive significant exposure to titanium tetrachloride except in the case of a spill or accident.

No analytical methods are currently available for measuring concentrations of titanium tetrachloride directly in any environmental medium, although methods are available for determining the concentrations of several of its hydrolysis products. As a result of the absence of detection methods for this compound, coupled with the compound's rapid rate of hydrolysis, titanium tetrachloride concentrations have not been reported in air, water, soil, sediments, or in food products.

Titanium tetrachloride has not been identified at any of 1,416 hazardous wastes sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1995). However, the number of sites evaluated for titanium tetrachloride is not known.

5.2 RELEASES TO THE ENVIRONMENT

Table 5-l summarizes data on industrial releases of titanium tetrachloride reported to the EPA (TR193 1995). These data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

5.2.1 Air

According to the Toxic Chemical Release Inventory (TR193 1995), an estimated total of 24,722 pounds of titanium tetrachloride, amounting to 99.6% of the total environmental release, was discharged to the air from 38 large manufacturing and processing facilities in the United States in 1993. Table 5-l lists the amount of titanium tetrachloride released from each of these facilities.

5.2.2 Water

No information was found regarding releases of titanium tetrachloride to surface water or groundwater via underground injection. However, assuming titanium tetrachloride spills may be dispersed with large amounts of water into a sewer system using recommended clean-up procedures (ITII 1984), runoff contaminated with titanium tetrachloride hydrolysis products could reach surface waters.

5.2.3 Soil

According to the Toxic Chemical Release Inventory (TR193 1995), an estimated total of 100 pounds of titanium tetrachloride, amounting to 0.4% of the total environmental release, was discharged to land from 38 large manufacturing and processing facilities in the United States in 1993. Table 5-l lists the amount of titanium tetrachloride released from each of these facilities.

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Titanium Tetrachloride

State [a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment [b]	POTW transfer	Off-site waste transfer
AL	AXIS	DU PONT							2,380,000
CA	ANTIOCH	DU PONT	1,140				1,140		
CT	NA	PFIZER INC.							
DE	EDGEMOOR	DU PONT	549				549		
GA	SAVANNAH	KEMIRA INC.	2,600				2,600		
KY	LOUISVILLE	AMERICAN SYNTHETIC RUBBER	5				5		
LA	LAKE CHARLES	HIMONT USA INC.	100				100		
LA	NORCO	SHELL NORCO MFG. COMPLEX	3,702				3,702		272,000
LA	WESTLAKE	LOUISIANA PIGMENT CO. L.P.	474				474		169
MD	BALTIMORE	SCM CHEMICALS	47				47		
MI	ADRIAN	ANDERSON DEVELOPMENT CO.	22				22		
MI	WESTON	AKZO CHEMICALS INC.	10				10		
MS	HAMILTON	KERR-MCGEE CHEMICAL CORP.	1,500				1,500		
MS	PASS CHRISTIAN	DU PONT DELISLE	3,070				3,070		
NJ	EDISON	AKZO NOBEL CHEMICALS INC.	1,100				1,100		
NJ	NA	E. I. DU PONT DE NEMOURS &							
NJ	WEST DEPTFORD TWP.	HUNTSMAN POLYPROPYLENE	1				1		
NV	HENDERSON	TITANIUM METALS CORP.	400				400		
NY	NA	CORNING INC.							
NY	NIAGARA FALLS	TAM CERAMICS INC.	23				23		
OH	ASHTABULA	SCM CHEMICALS	162				162		
OH	ASHTABULA	SCM CHEMICALS AMERICAS	100				100		
OK	BARTLESVILLE	PHILLIPS RESEARCH CENTER	1				1		
OR	ALBANY	OREGON METALLURGICAL	500				500		
PR	NA	PFIZER INC.							
TN	NEW JOHNSONVILLE	DU PONT	2,250				2,250		
TX	CHEEK	GOODYEAR TIRE & RUBBER	1	100			101		
TX	LONGVIEW	TEXAS EASTMAN DIV.	2,105				2,105		
TX	NA	AMOCO CORP.							
TX	NA	SOLVAY AMERICA INC.							

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Titanium Tetrachloride (continued)

State [a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment [b]	POTW transfer	Off-site waste transfer
TX	NA	CHEVRON CORP.							
TX	NA	NA							
TX	NA	OCCIDENTAL PETROLEUM							
TX	NA	E. I. DU PONT DE NEMOURS &							
TX	PASADENA	CATALYST RESOURCES	500				500		422
TX	PASADENA	ETHYL CORP.	4,248				4,248		
TX	WADSWORTH	OCCIDENTAL CHEMICAL CORP.	10				10		306,409
WV	GALLIPOLIS FERRY	AKZO NOBEL CHEMICALS INC.	2				2		
		Totals	24,622	100			24,722		2,959,000

Source: TRI93 1995

POTW = Publicly Owned Treatement Works

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Titanium tetrachloride hydrolyzes rapidly upon contact with moist air to form a vapor of hydrochloric acid, titanium dioxide, and titanium oxychloride (Whitehead 1983; Wilms et al. 1992). Consequently, environmental transport of this compound is negligible; however, the atmospheric transport of the resulting hydrolysis products may be significant.

No data were located to estimate the residence time for titanium tetrachloride in air or water; however, based on the compounds rapid hydrolysis, residence times are expected to be short (in the order of hours).

5.3.2 Transformation and Degradation

5.3.2.1 Air

Upon contact with moist air, titanium tetrachloride rapidly hydrolyzes with fuming into hydrogen chloride, titanium dioxide, and titanium oxychloride (Whitehead 1983; Wilms et al. 1992).

5.3.2.2 Water

When titanium tetrachloride is released to water it rapidly hydrolyzes to hydrochloric acid, titanium oxychloride, and titanium dioxide. Titanium oxychloride usually further hydrolyzes to hydrochloric acid and titanium dioxide (Wilms et al. 1992). In water, hydrochloric acid dissociates to the hydrogen and chloride ions. Titanium dioxide is insoluble in water and may settle out into the sediments.

5.3.2.3 Sediment and Soil

No information was located on the degradation of titanium tetrachloride released to soils or sediments; however, based on the rapid hydrolysis of this compound in moist air or in water, it may be expected that titanium tetrachloride will also hydrolyze upon contact with moisture in the soil and sediment. Residues of titanium dioxide, a very inert compound, are likely to remain in the soil or settle out to the sediment.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

No methods are currently available for measuring concentrations of titanium tetrachloride directly in any environmental medium. Methods are available for determining concentrations of several of its hydrolysis products (see Section 6).

5.4.1 Air

No information was located on concentrations of titanium tetrachloride in air.

5.4.2 Water

No information was located on concentrations of titanium tetrachloride in surface water or groundwater.

5.4.3 Sediment and Soil

No information was located on concentrations of titanium tetrachloride in sediment or soil.

5.4.4 Other Environmental Media

No information was located on concentrations of titanium tetrachloride in any other environmental media.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Information on the potential for general population exposure to titanium tetrachloride as a result of its manufacture, use, disposal, or presence at a hazardous waste site was not located. The lack of data on concentrations of titanium tetrachloride in air, water, soil, food, and other sources of general population exposure, coupled with the rapid rate of hydrolysis of titanium tetrachloride in all environmental media, suggest that such exposure is probably limited. Members of the general population are not likely to receive significant exposure to titanium tetrachloride except in the case of a spill or accident.

5. POTENTIAL FOR HUMAN EXPOSURE

Workers who are involved in the manufacture, processing, handling, and disposal of titanium tetrachloride are likely to be exposed to higher concentrations by dermal exposure and inhalation than the general population. Occupational exposure to titanium tetrachloride may be significant for workers in titanium industries. Preliminary data from a workplace survey, the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1980 to 1983, indicated that 2,107 workers, including 131 women, were potentially exposed to titanium tetrachloride in the workplace in 1980 (NIOSH 1993).

NIOSH (1992) does not provide recommendations for occupational exposure levels to titanium tetrachloride, but does provide a recommendation for occupational exposure levels to titanium dioxide, a hydrolysis product, of 0.2 mg/m^3. However, two independent limit setting organizations have recommended exposure limits for titanium tetrachloride. The American Industrial Hygiene Association's Workplace Environmental Exposure Limits (WEEL) Committee has recommended an S-hour TWA for chronic exposure of 0.5 mg/m^3 for titanium tetrachloride (AIHA 1994). In addition, the American Industrial Hygiene Association's Emergency Response Planning Guidelines Committee has recommended short-term (<1 hour) emergency limits (ranging from 100 mg/m^3 to 5 mg/m^3) (AIHA 1992).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in the titanium processing industry have the greatest potential for exposure to titanium tetrachloride during its production, processing, handling, and disposal. Workers who are involved in the process of producing titanium metal from titanium tetrachloride receive the most exposure, particularly those involved in the reduction process where they are exposed to vapors of titanium tetrachloride, titanium oxychloride, and titanium dioxide particulates (Garabrant et al. 1987). Maintenance and repair workers at these facilities also are exposed to high concentrations of titanium tetrachloride vapors containing its hydrolysis products, titanium oxide and hydrochloric acid (Mogilevskaja 1983). Workers who may use titanium tetrachloride for examining welding machinery also may be exposed as a result of occupational spills (Ross 1985).

Other than individuals who are occupationally exposed to titanium tetrachloride, no members of the general population are likely to receive high exposures except as a result of an accidental spill. Because of its rapid hydrolysis and because it has not been identified at any NPL hazardous waste site

(HazDat 1995), individuals living near these sites are unlikely to be exposed to any significant concentrations of titanium tetrachloride.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of titanium tetrachloride is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of titanium tetrachloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Although it has been determined that titanium tetrachloride hydrolyzes rapidly upon contact with water in all environmental media, it is not a well-defined chemical in terms of its physical and chemical properties (Merck 1989). Because of its rapid hydrolysis, information on some of its other chemical and physical properties would be difficult if not impossible to measure.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

5. POTENTIAL FOR HUMAN EXPOSURE

The available use, production, and release information for titanium tetrachloride is insufficient to determine the amount of titanium tetrachloride that hydrolyzes (CICIS 1993; OHM/TADS 1992; Whitehead 1983). In addition, there is a lack of data on how much titanium tetrachloride may be stored at waste sites, current methods of industrial disposal, and environmental releases that may result from its use as a dye, as a catalyst, and in the titanium metal industry. This information would be useful in determining whether significant releases of titanium tetrachloride occur, what disposal methods are available, and the potential of its hydrolysis products for environmental contamination.

Environmental Fate. Titanium tetrachloride readily hydrolyzes upon contact with moisture to form hydrochloric acid, titanium dioxide, and titanium oxychloride (Whitehead 1983; Wilms et al. 1992). Information on the degradation rates, persistence, and fate of these degradation products would be helpful in determining levels of titanium tetrachloride that may have an impact on various environmental media. This is particularly true for releases of titanium tetrachloride to soil as a result of spills.

Bioavailability. Available information regarding the rate of titanium tetrachloride absorption following inhalation, oral, and dermal contact has been discussed under Toxicokinetics (see Section 2.3) (Elo et al. 1972; Lee et al. 1986; Ophus et al. 1979; Redline et al. 1986). Information is lacking on the Bioavailability of titanium tetrachloride from environmental media as there is no information available on titanium tetrachloride concentrations in environmental media. Because of the physico-chemical properties of titanium tetrachloride, the major route of occupational exposure is by inhalation and the major target organ is the lung. Exposure can also occur by the dermal route particularly in cases of occupational spills. The rapid hydrolysis of titanium tetrachloride in water (Wilms et al. 1992) suggests that human exposure via contaminated drinking water or surface waters is unlikely, and no further studies on the bioavailability of this compound in water are indicated.

Food Chain Bioaccumulation. No information was found on the Bioaccumulation potential of titanium tetrachloride in aquatic or terrestrial ecosystems. However, its rapid hydrolysis upon contact with moisture (Wilms et al. 1992) suggests that there is little potential for Bioaccumulation or biomagnification in aquatic or terrestrial organisms. Further studies on the Bioaccumulation or biomagnification of this compound are not required.

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Exposure Levels in Environmental Media. No data were located on the concentration of titanium tetrachloride in ambient air or in occupational settings, therefore no estimate of inhalation exposure to titanium tetrachloride can be obtained for the general population or for any occupationally exposed groups. No data on the concentration of titanium tetrachloride in drinking water, surface water, or groundwater were located. However, because of its physico-chemical properties, titanium tetrachloride is expected to undergo rapid hydrolysis (Wilms et al. 1992) and would not be expected to be present in these environmental media.

Reliable monitoring data for the levels of titanium tetrachloride in contaminated media at hazardous waste sites are needed so that the information obtained on levels of titanium tetrachloride in the environment can be used in combination with the known body burden of titanium tetrachloride to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Most human exposures to titanium tetrachloride occur in the workplace as a result the production of titanium or because of accidental spills. No data on titanium tetrachloride concentrations in various human tissues and body fluids of unexposed populations, populations living near hazardous waste sites, or occupationally exposed groups are available. Because of its tendency to undergo rapid hydrolysis in aqueous environments, titanium tetrachloride is not likely to be detected in human tissues although particles of titanium dioxide, a hydrolysis product, have been detected in the lungs of occupationally exposed individuals (Elo et al. 1972; Ophus et al. 1979; Redline et al. 1986). Data on workplace exposures do exist (Garabrant et al. 1987; Ross 1985); however, exposure levels for the general population or persons living near hazardous waste sites are not available. Additional data on the concentrations of titanium tetrachloride hydrolysis products in body tissues and fluids are needed to estimate the extent of occupational exposure to this compound and in determining whether there is a health risk to occupationally exposed populations. Members of the general population are not likely to be exposed to titanium tetrachloride except in the case of a spill or accident.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for titanium tetrachloride were located. This substance is not currently one of the compounds for which a subregistry has been established in the

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National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

No ongoing studies on the potential for human exposure to titanium tetrachloride were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring titanium tetrachloride, its metabolites, and other biomarkers of exposure and effect to titanium tetrachloride. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Titanium tetrachloride hydrolyzes into titanium dioxide and hydrochloric acid upon contact with water or moisture in the air. Titanium tetrachloride cannot be detected in biological materials; however, titanium dioxide and titanium metal can be detected and may be used as indicators of exposure to titanium tetrachloride, although the presence of these materials in biological tissue does not necessarily mean the exposure occurred. See Table 6-l for a summary of the analytical methods most commonly used to detect titanium tetrachloride and titanium dioxide in biological materials. The primary method used to detect titanium dioxide in lung tissue is scanning and/or transmission electron microscopy (STEM). Electron probe X-ray microanalysis (EMX-SM) and energy dispersive X-ray analysis (EDXA) have been used in conjunction with STEM (Ferin et al. 1976; Redline et al. 1986). Sample preparation consists of fixation of the tissue sample in osmium tetroxide and/or glutaraldehyde, dehydration in ethanol, embedding in epoxy, followed by sectioning and staining with uranyl acetate and lead citrate'(Ferin et al. 1976; Ophus et al. 1979). These methods can detect particles as small as 0.2 μm.

No analytical methods were found for determining titanium dioxide in urine. However, titanium metal can be determined in urine by inductively coupled argon plasma, atomic emission spectroscopy

Table 6-1. Analytical Methods for Determining Titanium and Titanium Dioxide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (Ti metal)	Creatine determination, pH adjustment, addition of polydithiocarbamate resin, ashing of filter and resin, redissolution.	ICP-AES (NIOSH Method 8310)	0.02 ppm (wt/vol)	86 at 2 ppm (8% RSD).	NIOSH 1994a
Lung tissue (TiO_2 as particles)	Fixation in osmium tetroxide, dehydration in ethanol, embedding in epoxy, sectioning and staining with uranyl acetate and lead citrate.	TEM, EMX-SM; STEM	<0.2 µm	Not reported	Ferin et al. 1976
Lung tissue (TiO_2)	Drying of sample to constant weight followed by grinding.	OES	<100 ppm (wt/wt)	Not reported	Elo et al. 1972
Lung tissue (TiO_2 and Ti pigments)	Fixation of sample in glutaraldehyde and osmium tetroxide, dehydration in ethanol, embedding in epoxy resin, sectioning and staining with uranyl acetate and lead citrate.	TEM/EDS	Not reported	Not reported	Ophus et al. 1979
Lung tissue (TiO_2 and Ti pigments)	Dehydration of sample, mounting on carbon stub with carbon cement and coating with gold	SEM/EDS	Not reported	Not reported	Ophus et al. 1979
Lung tissue (TiO_2 and Ti pigments)	Ashing of sample followed by filtration of lung-tissue/ash dispersions through silver membrane	XD	Not reported	Not reported	Ophus et al. 1979

EMX-SM = electron probe X-ray microanalyzer; EDS = energy dispersive X-ray microanalysis; EDXA = energy dispersive X-ray analysis; ICP-AES = inductively coupled argon plasma, atomic emission spectroscopy; NIOSH = National Institute for Occupational Safety and Health; OES = optic emission spectrograph; RDS = relative standard deviation; SEM = scanning electron microscopy; STEM = scanning transmission electron microscopy; TEM = transmission electron microscopy; Ti = titanium; TiO_2 = titanium dioxide; wt/vol = weight/volume; wt/wt = weight/weight; XD = X-ray diffraction

(ICP-AES). This method is very sensitive, with a detection level of 20 ppb and a good recovery of 86% (NIOSH 1994a).

No information was located on detecting titanium dioxide in blood, adipose tissue, feces, or human milk.

6.2 ENVIRONMENTAL SAMPLES

No methods for detecting titanium tetrachloride in environmental samples were located. However, titanium dioxide may be used as an indicator of titanium tetrachloride's presence in air and some food samples, but its presence does not necessarily mean that titanium tetrachloride is or was present in the environmental sample. See Table 6-2 for a summary of the analytical methods used to determine titanium dioxide in environmental samples.

The primary method for detecting titanium dioxide in air is by gravimetric filter weight (G/FW) (NIOSH 1980, 1994b, 1994c) although gravimetric methods alone are not specific for titanium. Air sampling may be performed by collection of a sample on a polyvinyl chloride membrane or DM800 filter, drying or heating, followed by equilibration of the sample in an environmental chamber prior to measurement of the mass of particles collected. Detection limits are in the ppm range (NIOSH 1980, 1994b, 1994c). Spectroscopic methods can detect titanium metal in air at a detection level of 2 μg, and atomic absorption spectrophotometry (AAS) can detect titanium metal at 1.9 μg/mL for 1% absorption (Anonymous 1975). The corresponding limits of detection in air are dependent upon the volumes of both the air sample and the resulting extract. Samples for both methods are collected on an electrostatic precipitator (ESP), filter paper, standard impinger, or a membrane filter. The sample is reacted with hydrogen peroxide for the general spectrophotometric method, or acidified with hydrochloric acid solution for the AAS method (Anonymous 1975). Caution must be used for the general calorimetric method because iron, nickel, chromium, vanadium, molybdenum fluoride, and large amounts of phosphates and alkali metal sulfates can interfere (Anonymous 1975).-If these substances are present, additional fractionation steps will be needed. High levels of iron, aluminum, and fluoride enhance the response from titanium in the AAS method and this could result in an overestimation of the titanium concentration (Anonymous 1975). ICP-AES is an alternative method to determine titanium dioxide in air, with detection limits in the ppb range and an excellent recovery of 96% (NIOSH 1994d).

Table 6-2. Analytical Methods for Determining Titanium and Titanium Dioxide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (total particulates)	Collection of sample onto filter followed by drying and equilibration	G/FW (NIOSH Method 0500)	1.8 ppm (wt/vol) or 0.23 mg/m^3 for 133 L sample	100 (11% RSD) at 8 mg/m^3.	NIOSH 1994b
Air (respirable particulates)	Collection of sample onto filter followed by drying and equilibration.	G/FW (NIOSH Method 0600)	0.58 ppm (wt/vol) or 0.075 mg/m^3 for 400 L sample	Not reported	NIOSH 1994c
Air (Ti, TiO$_2$)	Collection of sample onto 0.8 µm filter, heating with ashing acid, dissolution of residue in dilution acid	ICP-AES (NIOSH Method 7300)	80 ppb for 100 L sample	96 at 2.5 µg/filter	NIOSH 1994d
Air (Ti metal)	Collection of sample with ESP, reaction with H$_2$O$_2$	Spectrophotometry	2 µg	Not reported	Anonymous 1975
Air (Ti metal)	Collection of sample with ESP, acidification	AAS	Instrument limit of detection = 1.9 µg/mL for 1% absorption; actual limit depends on sample and extract volumes	Not reported	Anonymous 1975
Cheese	Charring under IR lamp, ashing, addition of Na$_2$SO$_4$ and H$_2$SO$_4$	Spectrophotometry	Not reported	Not reported	Leone 1973

AAS = atomic absorption spectrophotometry; ESP = electrostatic precipitator; G/FW = gravimetric filter weight; H$_2$O$_2$ = hydrogen peroxide; H$_2$SO$_4$ = sulfuric acid; ICP-AES = inductively coupled argon plasma, atomic emission spectroscopy; IR = infrared; Na$_2$SO$_4$ = sodium sulfate; NIOSH = National Institute for Occupational Safety and Health; %RSD = percent relative standard deviation; Ti = titanium; TiO$_2$ = titanium dioxide; wt/vol = weight/volume

Hydrochloric acid is a hydrolysis product of titanium tetrachloride and can be detected in air. Gaseous hydrochloric acid must first be separated from aerosols that contain chloride ions. Filter packs, diffusion denuders, and diffusion samplers are the most common methods used to determined hydrochloric acid in air (Kamrin 1992). However, if hydrochloric acid is found in air, it is not necessarily indicative of exposure to titanium tetrachloride.

The presence of titanium dioxide in cheese has been studied (Leone 1973). Sample preparation included charring and ashing, followed by dissolution of the sample in sulfuric acid. A yellow-orange The addition of hydrogen peroxide to a cheese or air sample to calorimetrically determine titanium dioxide may cause interference from nickel, copper, cobalt, molybdenum, vanadium, and chromium, if present. It is unlikely, however, that these elements are present in cheese. Interferences in air samples can be overcome by the use of treated and untreated standards, or by precipitating the titanium dioxide (Anonymous 1975; Leone 1973).

No information was located on detecting titanium tetrachloride or titanium dioxide in water, soil, or sediment.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of titanium tetrachloride is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of titanium tetrachloride.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods exist for measuring titanium dioxide and titanium dioxide pigment, that is, different crystalline forms of titanium dioxide, in lung tissue (Elo et al. 1972; Ferin et al. 1976; Ophus et al. 1979) and for measuring titanium metal in urine (NIOSH 1994a). However, no methods were identified for detecting titanium tetrachloride in any biological materials. Most methods can only detect the presence and not the concentrations of titanium dioxide or titanium dioxide pigments in lung tissue (Elo et al. 1972; Ophus et al. 1979). STEM and EDXA methods cannot differentiate among different crystalline forms of titanium dioxide. However, X-ray diffraction (XD) methods can differentiate among the different crystalline forms and this information can be useful in the assessment of the bioavailablility of the titanium. However, no method exists for determining background levels of titanium tetrachloride or titanium dioxide in the general population, or levels at which biological effects occur.

More sensitive methods for detecting long-term exposure to titanium dioxide or titanium metal in biological tissue are desirable in order to monitor levels of titanium dioxide, titanium dioxide pigment, or metal in titanium industry workers. In addition, methods should be developed that could easily differentiate among the different crystalline forms of titanium dioxide in lung tissue so that possible differences in toxic effect resulting from differing bioavailabilities can be studied.

No biomarkers of effect of titanium tetrachloride exist. However, after a worker's accidental exposure to titanium tetrachloride, a dark pigmentation formed around the scars left by the burns, suggesting that titanium metal or titanium dioxide may be a biomarker of exposure (Lawson 1961). Additional study is required to determine the cause of the dark pigmentation. Further development of methods for determining biomarkers of effect for titanium tetrachloride would be beneficial to determine whether or not an individual has been exposed to the compound.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to titanium tetrachloride is most likely to result from being splashed with the liquid. Titanium dioxide, a hydrolysis product of titanium tetrachloride, or titanium metal in workplace air may be indicative of exposure to titanium tetrachloride, titanium metal, or titanium dioxide. G/FW is the most common method for determining titanium and titanium dioxide in air as particulate matter (NIOSH 1980, 1994b, 1994c), and spectroscopic methods are most common

for detecting titanium metal associated with particulates in air (Anonymous 1975; NIOSH 1994d). The sensitivity of the gravimetric methods is in the ppm range, and the sensitivity of the spectroscopic methods is in the ppb range with good recovery. Both methods can measure background levels in the environment and levels at which health effects may occur. A calorimetric method to determine the presence of titanium dioxide in cheese has also been developed (Leone 1973). The reliability and specificity of many of these methods have not been determined; therefore, methods to improve the reliability and specificity of titanium dioxide and titanium metal in air would be useful.

No methods for determining titanium tetrachloride or titanium dioxide in water, soil, or sediment were found.

6.3.2 Ongoing Studies

No ongoing studies regarding analytical methods were located for titanium tetrachloride.

7. REGULATIONS AND ADVISORIES

International, national, and state regulations and guidelines pertinent to human exposure to titanium tetrachloride are summrnarized in Table 7-l.

ATSDR has derived an intermediate-duration inhalation MRL of 0.01 mg/m^3 for titanium tetrachloride based on a mild lung dust cell reaction and increased relative lung weight in rats after intermittent exposure to titanium tetrachloride hydrolysis products for 4 weeks (DuPont 1979).

A chronic-duration inhalation MRL of 0.0001 mg/m^3 was derived for titanium tetrachloride based on its ability to cause irregular breathing and lung noises in rats, along with rhinitis, tracheitis, and alveolar hyperplasia (Lee et al. 1986).

Titanium effluent limitations are in effect for discharges from the production of titanium at primary and secondary titanium facilities. The following existing point sources are subject to regulation: chlorination off-gas wet air pollution control, titanium tetrachloride handling wet air pollution control, reduction area wet air pollution control, melt cell wet air pollution control, chlorine liquefaction wet air pollution control, sodium reduction container reconditioning wash water, chip crushing wet air pollution control, acid leachate and rinse water, sponge crushing and screening wet air pollution control, acid pickle and wash water, scrap milling wet air pollution control, scrap detergent wash water, casting crucible wash water, and casting contact cooling water (EPA 1985a).

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Titanium Tetrachloride

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
WHO	No information given		WHO 1984
NATIONAL			
Regulations:			
a. Air:			
EPA OAQPS	LOC - Levels of Concern for Each HAP	1.00 mg/m^3	59 FR 15504 40 CFR 63.44 EPA 1994
	Short-term "demininis" Value for Each HAP	0.00159 lbs./hr	59 FR 15504 40 CFR 63.44 EPA 1994
EPA OERR	Regulated Toxic Substances and Threshold Quantities for Accidental Release Prevention	2,500 lbs.	40 CFR 68.130 EPA 1994
	List of Extremely Hazardous Substances and Their Threshold Planning Quantities	100 lbs.	40 CFR 355 Appendix A EPA 1987
b. Other:			
EPA OERR	Reportable Quantity (proposed)	100 lbs.	58 FR 54836 40 CFR 302.4 EPA 1993
	Toxic Chemical Release Reporting: Community-Right-To-Know	Yes	40 CFR 372.65 EPA 1988a
Guidelines:			
a: Air:			
NIOSH	Extremely Hazardous Substances and Data for Hazards Analysis Level of Concern	0.001 mg/m^3	NIOSH 1992
STATE			
Regulations and Guidelines:			
a. Air:	Average Acceptable Ambient Air Concentrations		NATICH 1992
TX	30 minutes Annual	1.00x10^1 µg/m^3 1.00x10^1 µg/m^3	

CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FR = Federal Register; HAP = Hazardous Air Pollutant; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute of Occupational Safety and Health; OAQPS = Office of Air Quality Planning and Standards; OERR = Office of Emergency and Remedial Response; WHO = World Health Organization

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)--The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity- T h e occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In Viva-Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$)-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration $_{(50)}$ (LC$_{50}$)-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD$_{LO}$)-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD$_{50}$)-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$)-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biolsgically significant increases in frequency or severity of adverse effests seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K$_{OW}$)-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1^* -The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and μg/m^3 for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD$_{50}$)-A calculated dose of a chemical, introduced by a route other than-inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

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.

APPENDIX A

<u>Dose and end point used for MRL derivation</u>: 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

<u>Uncertainty Factors used in MRL derivation</u>:

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

<u>Was a conversion factor used from ppm in food or water to a mg/body weight dose?</u> No

<u>If an inhalation study in animals, list conversion factors used in determining human equivalent dose:</u>
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 x RDDR$_{TH}$

      = 5 mg/m^3 x 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$_{HEC}$ ÷ UF

      MRL = 1.032 mg/m^3 ÷ 90

      MRL = 0.01 mg/m^3

<u>Was a conversion used from intermittent to continuous exposure?</u> No

APPENDIX A

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

APPENDIX A

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

APPENDIX A

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-1 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

APPENDIX A

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)   <u>Route of Exposure</u> One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-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.

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(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.

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(11)   <u>CEL</u> 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)   <u>Footnotes</u> 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)   <u>Exposure Period</u> 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)   <u>Health Effect</u> These are the categories of health effects for which reliable quantitative data
          exists. The same health effects appear in the LSE table.

(15)   <u>Levels of Exposure</u> 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)   <u>NOAEL</u> 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)   <u>CEL</u> 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)   <u>Estimated Upper-Bound Human Cancer Risk Levels</u> 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)   <u>Key to LSE Figure</u> The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

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

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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**

Acute (≤14 days)

Intermediate (15-364 days)

Systemic

Systemic

14 →

15 → (ppm)

Death, Respiratory, Hematological (Acute)

Death, Respiratory, Hematological, Hepatic, Reproductive, Cancer* (Intermediate)

10000

1000

100

10

1

0.1

0.01

0.001

0.0001

0.00001

0.000001

0.0000001

16r 17r 24g 18r 18r 20m 22g 21r 20m

31r 30r 33r 28m 22m 29r 35m 37m 34r 34r 27r 40m 38r 39r

16 →

17 →

18 → Estimated Upper Bound Human Cancer Risk Levels

10^{-4}

10^{-5}

10^{-6}

10^{-7}

19 →

Key

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

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

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

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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
$\geq$	greater than or equal to
=	equal to
<	less than
$\leq$	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram