

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 2-minute inhalation LC₅₀ values in rats exposed head-only were 460 mg/m³ and 108,000 mg/m³, respectively (DuPont 1980); other LC₅₀ 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

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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/m³ 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 2-1 and plotted in Figure 2-1.

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 2-1 and plotted Figure 2-1.

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

Key to figure	a 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/m ³)	LOAEL		Reference
					Less serious (mg/m ³)	Serious (mg/m ³)	
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	10M (increased urine pH and decreased osmolality)		
			Endocr	40 M			
			Dermal	40 M			
			Ocular	40 M			
			Bd Wt		40M (19% reduction in body weight gain)		
CHRONIC EXPOSURE							
Systemic							
6	Rat (Cr: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	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m ³)	LOAEL		Reference
					Less serious (mg/m ³)	Serious (mg/m ³)	
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 TiCl ₄ 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)

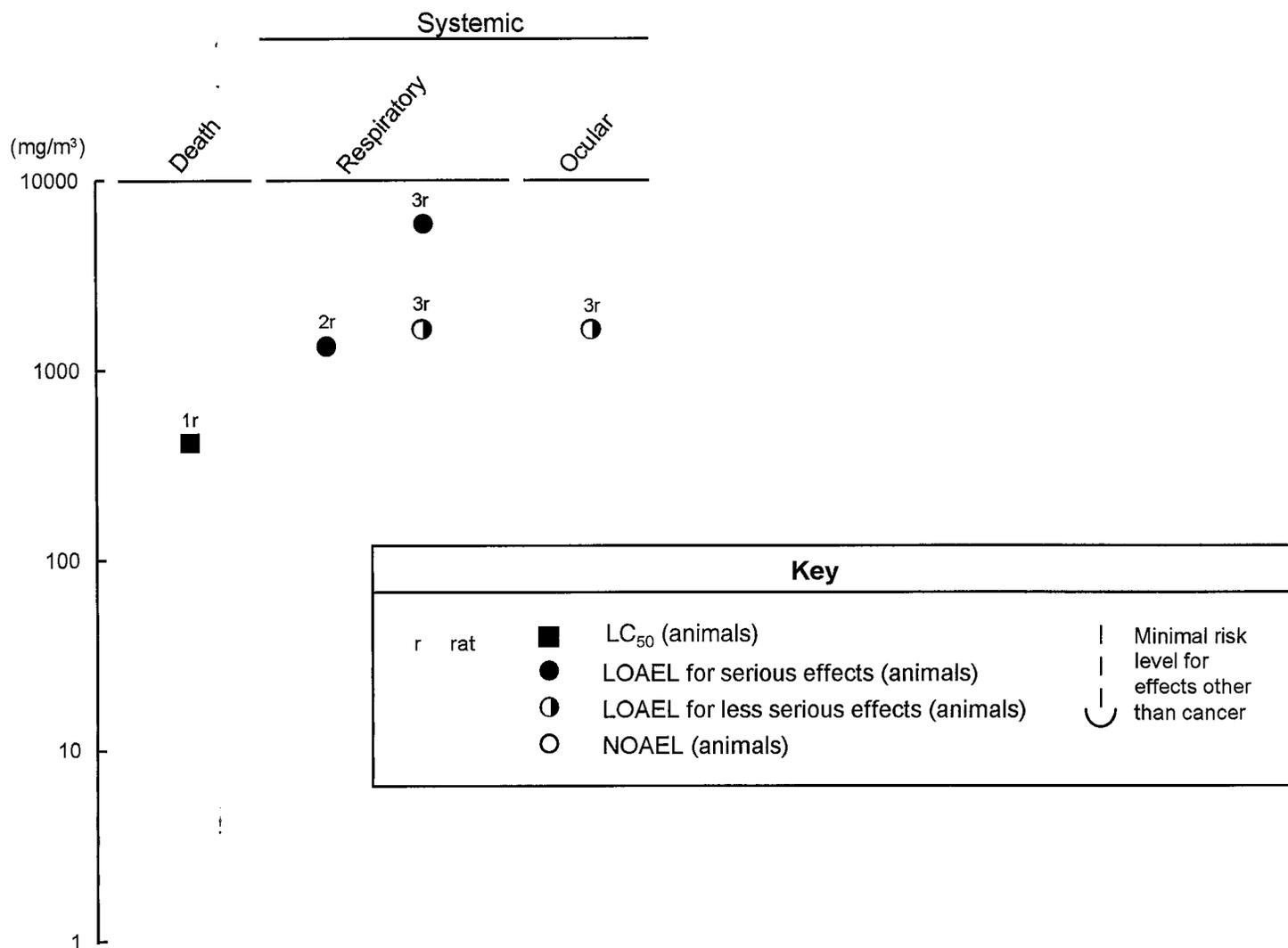


Figure 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)
Intermediate (15-364 days)

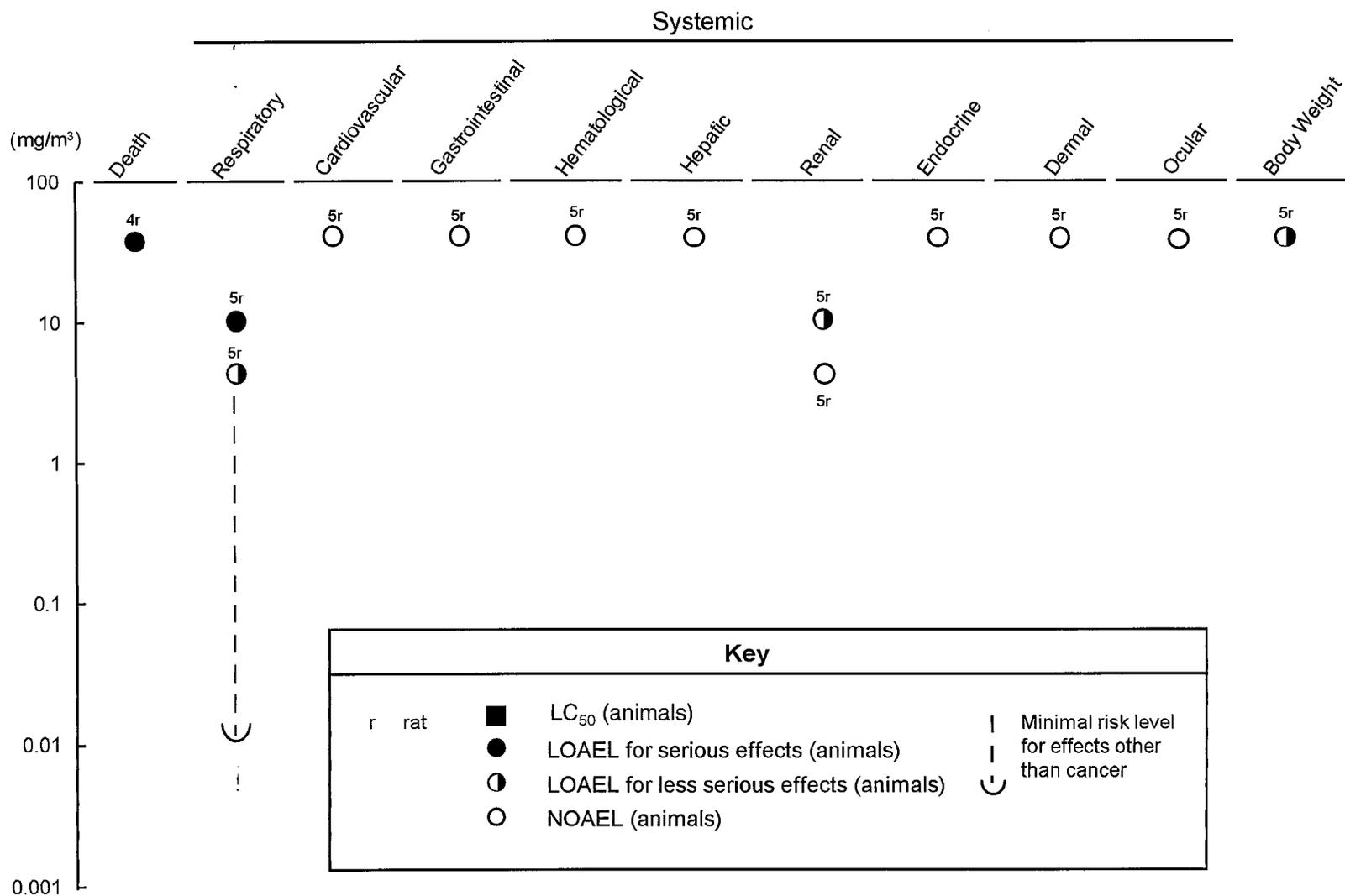
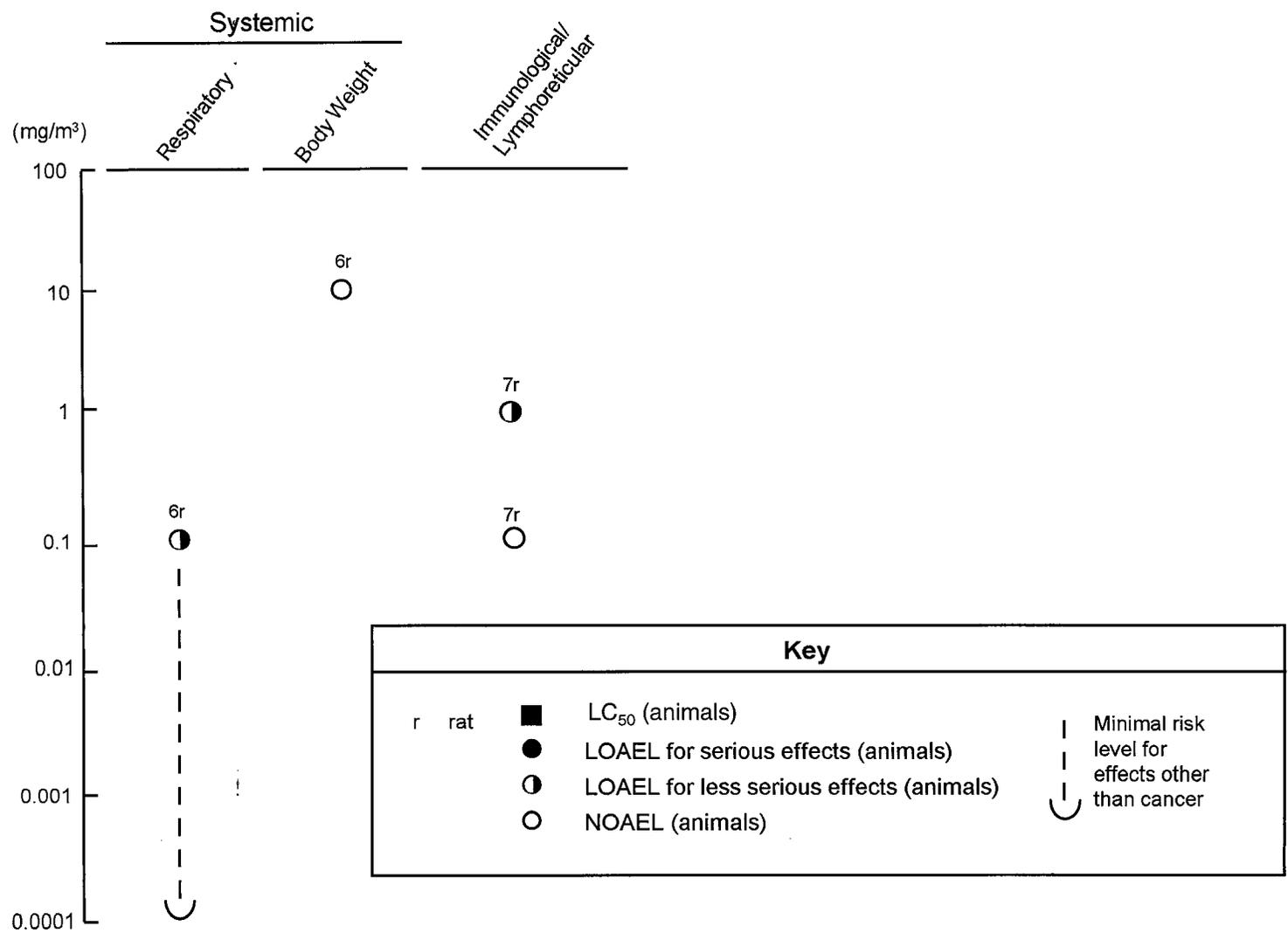


Figure 2-1. Levels of Significant Exposure to Titanium Tetrachloride - Inhalation (continued)
Chronic (≥ 365 days)



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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/m³). 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/cm³ 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/m³ 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/m³, 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/m³ 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/m³) 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/m³ exposure level is considered a less serious LOAEL and was used to derive an intermediate-duration inhalation MRL of 0.01 mg/m³, as described in the footnote in Table 2-1.

In a chronic inhalation study, groups of 100 CrI:CD rats/sex/concentration were exposed by inhalation to 0, 0.1, 1.0, and 10.0 mg/m³, 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/m³, 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 were 0-2.5%, 12-20%, 41-49%, and 30-44% for the control, low-, mid-, and high-exposure groups, respectively. The 0.1 mg/m³ 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

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($p < 0.05$) 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 2-1.

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, neutrophils, 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

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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/m³ 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/m³ 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/m³ 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/m³ 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 parameters returned to pre-exposure levels after a 2-week recovery period. An exposure level of 5 mg/m³ 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.

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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/m³ 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/m³ 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 burns 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/m³ 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

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(females not tested) exposed to up to 40 mg/m³ 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/m³ 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/m³, did not alter body weight gain. Body weight from Crl:CD rats exposed to 0, 0.1, 1.0, and 10.0 mg/m³ 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/mm³ 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 burns 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

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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 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/m³ 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/m³ 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/m³ of hydrolyzed titanium tetrachloride. Dose-related changes observed in the tracheobronchial lymph nodes of rats exposed to 1.0 and 10.0 mg/m³ 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.

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All NOAEL and LOAEL values from each reliable study for immunological effects in rats in chronic duration studies are recorded in Table 2-1 and plotted Figure 2-1.

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/m³ 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 2-1 or Figure 2-1.

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/m³ titanium tetrachloride (DuPont 1979). Female rats were not tested in this study. The 40 mg/m³ 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 2-1.

2.2.1.6 Developmental Effects

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

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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 $<0.5\text{-}3.0\text{ mg/m}^3$ 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

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were found. Well-differentiated squamous cell carcinoma was found in 1 of 75 males and 2 of 75 females exposed to 10.0 mg/m³ 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.

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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.

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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 45-year-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/cm³ of tissue. Further analysis showed that the particulates contained various metallic alloys: 61% of the particulates consisted of aluminum and other metals such as

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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 exothermic, 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 burns in all three workers. In all three cases, the most severe burns occurred in areas that were occluded by either belts or shoes. The burns 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 burns to transitory erythema. It is postulated that the initial thermal burn exposes the deeper tissue layers to the effects of hydrochloric acid, resulting in more severe burns 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

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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 burn, 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 burn, which then exposes the deeper tissue layers to other titanium tetrachloride hydrolysis products such as hydrochloric acid, resulting in even more severe and deeper burns. In other words, the extremely serious effects observed following exposure to titanium tetrachloride are the result of combined thermal and acid burns (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 burn. 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 burn 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 burns were identified. Grade I and grade II eye burns resolve without complications, while grade III and grade IV burns result in eye loss. Grade I eye injuries usually consist of mild defects of inferior corneal 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

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take longer to heal. No information on grade III eye injuries was given. The grade IV eye injuries have corneal and conjunctival burns accompanied by conjunctival ischemia and lens opacity. Over a period of time (up to 2 months), this injury progresses to severe corneal stromal lysis and ultimately corneal 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/mm³ 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 burns 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 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* 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

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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: >0 to $< 5.0 \text{ mg/m}^3$, 5.0 to $< 10 \text{ mg/m}^3$, 10 to $< 20 \text{ mg/m}^3$, and $> 20 \text{ mg/m}^3$. 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

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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 titanate (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).

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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/m³ 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

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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/m³ 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 burns 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.

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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 (perspiration 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 burns. In other words, the extremely serious effects observed following exposure to titanium tetrachloride are the result of combined thermal and acid burns (Chitkara and McNeela 1992).

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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 11-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/m³ 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/m³ 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/m³ 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/m³ 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/m³ for tracheitis and rhinitis seen in groups of 100 male and female Crl:CD rats exposed to 0.1, 1.0, or 10 mg/m³ 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 ($p < 0.001$). 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 0.1-0.4- 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 45-year-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/m³ 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

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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 burns. The most severe burns in reported cases occurred in the areas that were occluded by either belts or shoes (Lawson 1961). These burns 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 it 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 burns. 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 burns were identified based on the description of eight cases of accidental occupational exposure (Chitkara and McNeela 1992). Grade I and grade II eye burns resolve without complications, while grade III and grade IV burns result in eye loss. Grade I eye injuries usually consist of mild defects of inferior corneal 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

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heal. No information of grade III eye injuries was given. The grade IV eye injuries have corneal and conjunctival burns 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 45-year-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 11-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/m³ titanium tetrachloride for 4 weeks (DuPont 1979); no further

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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/m³ 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 (Tsuji 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, TA100, 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				
<i>Salmonella typhimurium</i> (TA1537, TA2637, TA98, TA100)	Gene mutation	NT	–	Ogawa et al. 1987
<i>S. typhimurium</i> (TA1537, TA2637)	Gene mutation	NT	– ^a	Ogawa et al. 1987
<i>Bacillus subtilis</i> (H17, M45)	DNA damage	NT	–	Kada et al. 1980; Kanematsu et al. 1980

^aBacterial strains were simultaneously exposed to titanium tetrachloride and 9-aminoacridine.

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

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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.

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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

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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 0.1-0.4 μ m-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 burns 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 burns.

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).

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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).

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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 1-2 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.

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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.

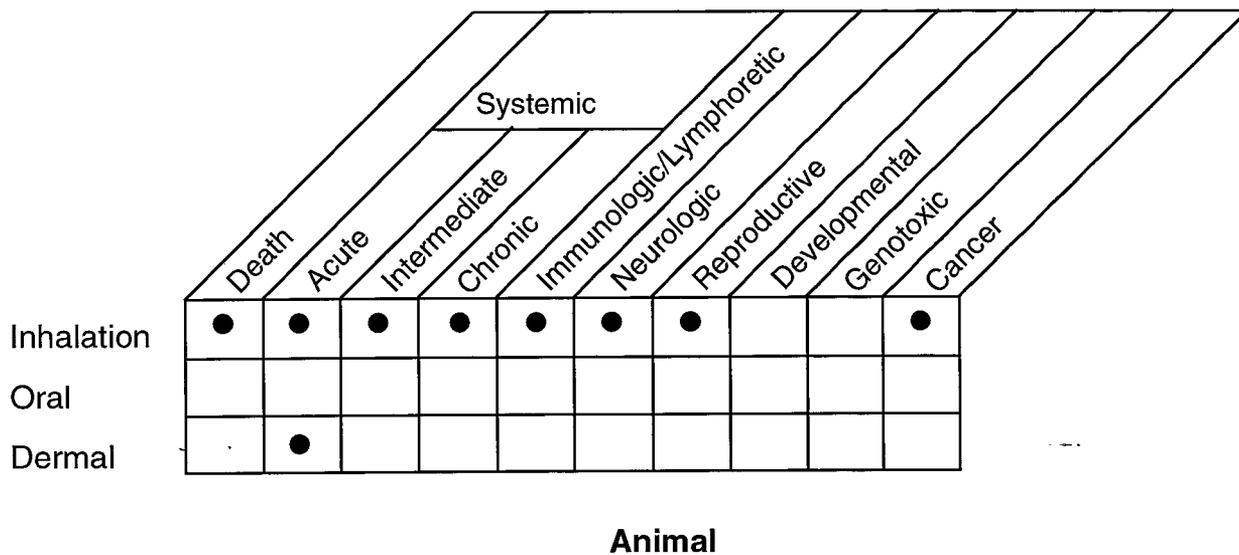
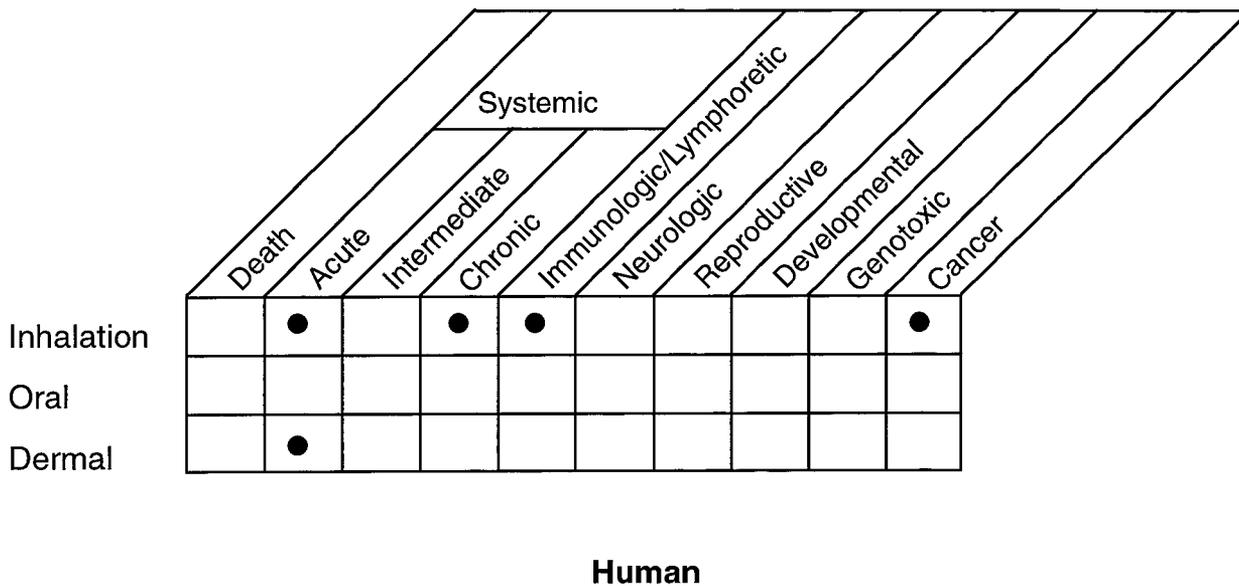
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean 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 Profiles*

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



● Existing Studies

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(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

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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 and 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

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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

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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

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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 burns 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 1-2 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).

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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).

