ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR TITANIUM TETRACHLORIDE

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March 2014

CONTENTS

ADDENDUM FOR TITANIUM TETRACHLORIDE Supplement to the 1997 Toxicological Profile for Titanium Tetrachloride

Background Statement

This addendum to the Toxicological Profile for Titanium Tetrachloride supplements the profile that was released in 1997.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator will "establish and maintain an inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and to federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature in a fashion utilizing the process of Systematic Review. Systematic Review procedures were used to enhance transparency for reaching and communicating evidence assessment conclusions. This addendum is meant to revise, update, and replace only the health effects section of the original profile from 1997. Since new studies are scarce, the information previously included in the Health Effects section of the Toxicological Profile is here presented in the new format for consistency.

Chapter numbers in this addendum coincide with the Toxicological Profile for Titanium Tetrachloride (1997). This document should be used in conjunction with the profile. It does not replace it.

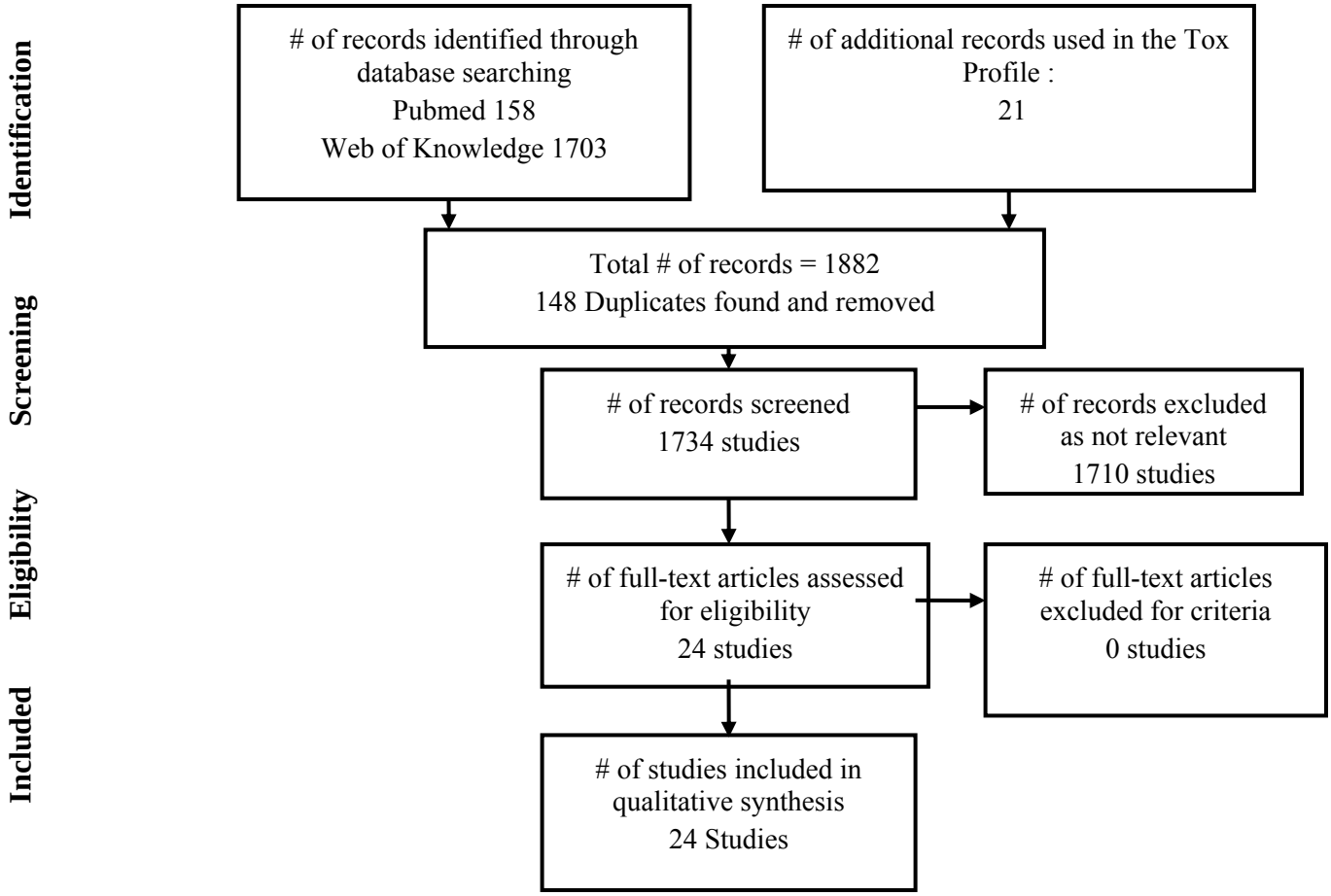
Study Design Overview

In this addendum, we used the concepts of Systematic Review as a means to enhance transparency, consistency, and efficiency in conducting our literature-based evaluations. Systematic Review is a scientific investigation that focuses on a specific question, and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies (Institute of Medicine 2011, NTP 2013). The flow chart presented in Figure 1 illustrates the results of Identification, Screening, Eligibility and studies Included. We searched PubMed and Web of Knowledge through March 2013, as well as documents from EPA, using the CAS number for Titanium Tetrachloride (CAS# 7550-45-0) and MESH terms for the chemical. Abstract and PDF screening was used to assign the studies to the relative chapter. The eligibility criteria were reports of Titanium Tetrachloride related to: health outcomes; toxicokinetics; population exposure; genotoxicity; mechanism of action. Of the 1734 studies included in the screening, only 24 were eligible for full-text analysis. Due to the paucity of new data for titanium tetrachloride, the studies identified and reviewed in the 1997 toxicological profile were included in the data tables provided in the addendum. Only three new studies matching the criteria were identified in the literature search. The data extraction strategy follows the NTP Guidance on Systematic Reviews (NTP 2013).

For more detailed discussions of the protocol, please see Appendix 1.

This addendum was developed in collaboration with the National Institute of Environmental Health Sciences National Toxicology Program's Office of Health Assessment and Translation.

Figure 1: Flow Chart of Study Selection for Titanium Tetrachloride



2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.1 Death

No new data were identified with regards to inhalation exposure to titanium tetrachloride and the health outcome of death.

See below for studies previously evaluated.

Table 1. Summary table – Inhalation

Reference, design	Results
Chitkara and McNeela 1992 (United Kingdom) **Human Study** **Study Design:** Case Report **Exposure**: One-Time occupational exposure accident **Study Summary:** Eight cases of $TiCl_4$ burns to the eye, which have been seen in the casualty department over the past 4 years, four of which illustrate this compound's propensity for severe tissue damage.	Patient 8 (Male, Unknown Age) – Whole body Splash; Extensive burns to facial skin, nasopharynx and larynx; Corneas thick and opaque and extensive swelling of bulbar conjunctiva and episclera; some clearing of corneal opacification in right eye after 14 days, but not in left; severe injury to lungs by inhalation; progressive deterioration in pulmonary compliance; died 2 weeks after injury
EPA 1990b (United States) **Human Study** **Study Design:** Nested case-control **N**= 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; Less than 1 year to over 5 years **Study Summary:** Study examined incidence of and mortality (between 1935-1983) from lung cancer in workers exposed to titanium tetrachloride ($TiCl_4$); controls are population-based **Reanalysis of data from Chen & Fayerweather cohort	Outcome: Lung Cancer Mortality Exposure Level: Control; Case N per group: 96; 24 aOR (90% CI): Ref; 1.1 (0.4, 3.2) Adjusted for age, smoking status, year of hire, pay class, and geographic location **Conclusions:** No increase in mortality from any cause.
Fayerweather et al. 1992 (United States) **Human Study** **Study Design:** Nested Case-Control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; Less than 1 year to over 5 years. **Study Summary:** A total of 2477 employees from two titanium dioxide plants were studied. Of that group, 969 employees exposed to titanium tetrachloride were observed from 1956 through 1985 for cancer and chronic respiratory disease incidence	Outcome: Lung Cancer Exposure Level (mg/m3): Referent (0); High (>3.0) N per group: 79; 20 aOR (90% CI): Ref; 1.2 (0.3, 4.0) Adjusted for age, smoking status, employment history and Titanium Dioxide **Conclusions:** Nested case-control analyses found no statistically significant association between titanium tetrachloride exposure and risk of lung cancer, chronic respiratory disease, and chest roentgenogram abnormalities. No cases of pulmonary fibrosis were observed among titanium tetrachloride-exposed employees.

Table 1. Summary table – Inhalation

Reference, design	Results
	Smoking was found to be a strong predictor of lung cancer mortality in the non-exposed employees with an increased risk of dying from lung cancer up to 7-fold higher in current smokers than in nonsmokers.
DuPont 1980 **Species/Strain/Sex:** Rats/Crl-CD/Male **N=** 24; 6 rats/group, 4 groups/exposure time **Exposure:** Inhalation Exposure, head only, single exposure; 460 – 108,000 mg/m^3 for 2-240 minutes **Study Summary:** LC50 study **Endpoint:** Death (LC50)	Median Lethal Concentration (LC50) Exposure Time Minutes / Mean Exposure mg/m^3 / Lower 95% CI / Upper 95% CI 2 / 108000 / 99000 / 139000 5 / 36000 / 29000 / 54000 15 / 5500 / 3700 / 8500 30 / 3000 / 1800 / 3900 60 / 1300 / 1000 / 1600 120 / 1100 / 750 / 1400 240 / 460 / 380 / 530 Outcome / Time / Effects Pathology Study / 2, 5, 15, 30, 240 minutes / similar lesions seen in rats which died during or immediately after experiment; air passages were inflamed and showed hypermucous secretion, epithelial denudation, severe necrotic laryngitis, pulmonary congestion and hemorrhage; death probably induced by pulmonary edema 30 minutes; autopsied after 1,3,7,21,49 days of recovery / 1 day post- severe respiratory inflammation; 3 days- respiratory-inflammatory exudate was already organizing; 7 days-acute inflammation had subsided and denuded epithelium was partially repaired; 14- & 21 days-lesions had almost disappeared and damaged epithelium had repaired; 49 days-respiratory tract showed normal architecture **Conclusions:** Median lethal concentrations were determined for 7 exposure times; Autopsies showed acute inflammation of the respiratory tract and eye; cause of death appeared to be pulmonary edema
Mezentseva et al. 1963 **Species/Strain/Sex:** Mice/NR/NR **N** = 15; 5 mice/group; no controls **Exposure:** Inhalation Exposure, single exposure; 2 hours. **Study Summary:** White mice were exposed for 2 hours to HCl or the hydrolysis products of $TiCl_4$ (titanium oxychloride, titanium dioxide and hydrochloric acid).	**Conclusions**: Hydrolysis products gave rise to higher animal mortality (9/15 died) than pure HCl (only 1 fatality), but HCl had a stronger local effect on the upper respiratory tract and on necrosis of the conjunctiva. The hydrolysis products demonstrated a higher toxicity in causing edema in the lungs.

Table 1. Summary table – Inhalation	
Reference, design	**Results**
DuPont 1979 **Species/Strain/Sex:** Rats/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3.	Exposure Level / N / Death / Mean (mg/m3) / Standard Deviation Controls 25 0 0 0 Low 25 0 4.9 0.9 Intermediate 25 0 10 1.9 High 25 2 40 5.9 **Results/Conclusion**: 2 rats from the highest exposure group died on days 15 and 23 of exposure; the cause of death appeared to be the result of respiratory failure.

2.2.1.2 Systemic Effects

No new data were identified with regards to inhalation exposure to titanium tetrachloride and systemic effects. See below for studies previously evaluated.

Respiratory Effects:

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
Lawson 1961 (United States) **Human Study** **Study Design:** Cohort **N** = 10 **Exposure:** Occupational – Chronic **Study Summary:** Plant workers with 4+ year's exposure to fumes **Endpoint:** Respiratory biochemistry	No significant changes in weight; mild eosinophilia in 3 and relative lymphocytosis in 4; all but 1 had adequate vital capacities-this man was 78% of normal; one subject's chest x-rays showed an abnormality which consisted of fibrotic and infiltrative changes at the left base with areas of discoid atelectasis
Ross 1985 **Human Study** **Study Design:** Case Report **N** = 3 **Exposure:** Occupational – Acute **Study Summary:** Research workers were using $TiCl_4$ to assess a welding torch. Brass tap flew off filling the room with fumes. **Endpoint:** Respiratory biochemistry	One worker complained of ticklish cough accompanied by unpleasant taste. Another developed cough and felt tightness in chest, along with eye irritation for 2 hours post exposure. Third worker experience no symptoms. None were severe, medical examination several hours later revealed no abnormalities. There were skin lesions and marked congestion of mucous membranes of pharynx, vocal cords and trachea; lesions healed with scarring
Park et al. 1984 (United States) **Human Study** **Study Design:** Case Report **Exposure**: Occupational – Acute **Study Summary:** 50-yr old chemical engineer was admitted to the ICU in respiratory failure after industrial accident.	The patient developed delayed complications from inhalation of products produced from the hydrolysis of $TiCl_4$

Table 1 – Summary table – Inhalation

Reference, design	Results
Exposed for about 2 minutes to the vapor from a cloud that had formed when TiCl4 was exposed to the air **Endpoint**: Respiratory pathology	
Garabrant et al. 1987 (United States) **Human Study** **Study Design:** Cross-sectional survey of titanium metal production workers **N** = 209; maintenance workers (n = 58) mean age 42.3 years; chipping and washing workers (n = 73) mean age 35.0 years; and titanium tetrachloride reduction workers (n = 78) mean age 34.5 years **Exposure**: Occupational – Chronic; **Determination of Exposure:** Reduction workers were defined as those who had spent at least six months in the reduction area. Chipping and washing workers were defined as those who had spent at least six months in the chipping and washing area but who had spent less than six months in the reduction area. Maintenance and service workers were defined as those who had spent less than six months in production jobs (reduction or chipping and washing) **Endpoint**: Respiratory pathology **Reviewed in NIOSH 1980	<table><tr><th></th><th>Maintenance (Control)</th><th>Chipping & Washing</th><th>Reduction</th></tr><tr><th>Outcome</th><th>N outcome/N total</th><th>N outcome/N total</th><th>N outcome/N total</th></tr><tr><td>Pleural Disease</td><td>12/58</td><td>16/73</td><td>8/78</td></tr><tr><td>Opacities Profusion</td><td>4/58</td><td>3/73</td><td>2/78</td></tr></table> **Conclusion:** No significant differences in the prevalence of symptoms between the different groups. Pleural disease was strongly associated with duration of work in titanium manufacturing and with previous asbestos exposure; no significant differences in pulmonary function, symptom prevalence, abnormalities revealed in physical exam or pulmonary function between subjects who had pleural thickening and those who did not. Using M&S workers as control may have led to underestimation
Elo et al. 1972 (United States) **Human Study** **Study Design:** Case Report **N =** 3 **Exposure**: Occupational – Chronic **Study Summary:** Tissue was obtained from 3 workers who were employed in a factory that processed TiO2; 2 taken at thoracotomy, 1 taken at autopsy **Endpoint:** Respiratory pathology	Patient 1 (Male, 37-yrs old) – Working for 10 yrs; 8.5 years in dusty work; recurrent episodes of bronchitis over past several years; dyspnea and other symptoms aggravated by dusty environment; symptoms gradually increased greatly in severity; spirometry and oxyergometry revealed no significant abnormalities; minimal changes indicating pneumoconiosis; readmission to hospital-lower lobe found to be adherent to parietal pleura and diaphragm; lung surface full of patches showing carbon pigment Patient 2 (Male, 52-yrs old) – employed for 9 years; 6 in dust conditions; last 3 yrs, recurring episodes of productive cough increasingly associated with dyspnea; heavy smoker; radiological examination showed fibrotic changes in both lungs and changes which suggested pneumoconiosis; secretion found on bronchi; biopsy from mucosa showed nonspecific bronchitis; right thoracotomy – lung free of adhesions and showed carbon-like pigment throughout the surface; vesicular emphysema, especially in apical segment of upper lobe Patient 3 (Male, 38-yrs old) – employed 9 years, all in dusty departments; Medicolegal autopsy performed; no pleural adhesions, but green-colored pleural changes were most pronounced in posterior parts of upper lobes; cross section – patches and strands consisting of greenish aggregations; found a few slightly enlarged lymph nodes- mainly anthracotic in appearance; definite pulmonary fibrosis subpleurally **Conclusions:** all cases showed carbon-like, but birefractive pigment aggregations which formed extensive patches subpleurally; all 3 lung tissues showed considerable amounts of titanium

<table>
<tr><th colspan="2">Table 1 – Summary table – Inhalation</th></tr>
<tr><th>Reference, design</th><th>Results</th></tr>
<tr><td>Redline et al. 1986 (United States)

Human Study
Study Design: Case Report
Exposure: Occupational – Chronic (13 years)
Study Summary: A 45 year old black man had been well until five years previously (1978) when he noted progressive dyspnea associated with a non-productive cough. Respiratory symptoms, which initially occurred only at work, were subsequently experienced throughout the day. He had no known exposure to individuals with tuberculosis and had no other medical problems.
Endpoint: Respiratory pathology</td><td>A patient presented with granulomatous lung disease associated with the pulmonary deposition of various metallic particles

Conclusions: chest radiograph-diffuse bilateral fibronodular infiltrates. Transbronchial biopsy from right lower lobe showed multiple non-caseating granulomas containing numerous birefirengent crystals.</td></tr>
<tr><td>Karlsson et al. 1986

Species/Strain/Sex: Rat/Sprague-Dawley/Female
N = 12; 3 juvenile rats/exposure concentration
Exposure: Inhalation Exposure, single exposure to 1466, 5112, 7529, and 11492 mg/m3 for 10 minutes.
Study Summary:
Acute inhalation of pure $TiCl_4$ – 10-minute exposure at different concentrations of Ti
Endpoint: Respiratory pathology</td><td>10-minute exposure: Animals exposed to the highest concentrations showed wet noses, nasal discharge and swollen eyelids; most animals appeared normal 24-48 hrs after exposure. Lungs from exposed animals showed no gross changes compared to controls - some microscopic changes in animals exposed to high concentrations.

<table><tr><th>Concentration (mg $TiCl_4/m^3$)</th><th>Nasal discharge, Dyspnea</th><th>Discrete Inflammatory Residues (# with outcome/total n)</th></tr><tr><td>1466</td><td>3/3</td><td>0/3</td></tr><tr><td>5112</td><td>3/3</td><td>0/3</td></tr><tr><td>7529</td><td>3/3</td><td>1/3</td></tr><tr><td>11,492</td><td>3/3</td><td>2/2</td></tr></table>
Conclusion: All animals at the different levels showed marked signs of irritation; all animals showed an essentially normal lung picture after 7 days</td></tr>
</table>

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1980 **Species/Strain/Sex:** Rat/Crl-CD/Male **Exposure:** Inhalation Exposure, head only, single exposure; 460 – 108,000 mg/m^3 for 2-240 minutes **Endpoint:** Respiratory pathology	Outcome / Doses / Effects Pathology Study; 2, 5, 15, 30, 240 minutes; similar lesions seen in rats which died during or immediately after experiment; air passages were inflamed and showed hypermucous secretion, epithelial denudation, severe necrotic laryngitis, pulmonary congestion and hemorrhage; death probably induced by pulmonary edema 30-minute exposure; 30 minutes; autopsied after 1,3,7,21,49 days of recovery; 1 day post- severe respiratory inflammation; 3 days- respiratory-inflammatory exudate was already organizing; 7 days-acute inflammation had subsided and denuded epithelium was partially repaired; 14- & 21 days-lesions had almost disappeared and damaged epithelium had repaired; 49 days-respiratory tract showed normal architecture **Conclusions:** Autopsies showed acute inflammation of the respiratory tract and eye; cause of death appeared to be pulmonary edema
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Respiratory pathology ****Information used to derive Minimal Risk Level (MRL) for Intermediate Inhalation Exposure** Dose and end point used for MRL derivation: The 5 mg/m^3 exposure concentration is considered a less serious LOAEL for mild dust cell reaction and increased relative lung weight. Uncertainty Factors used in MRL derivation: 3 for use of a minimal LOAEL 3 for extrapolation from animals to humans 10 for human variability $LOAEL_{HEC} = LOAEL \times RDDR_{TH} = 5\ mg/m^3 \times 0.2064 = 1.032\ mg/m^3$ where: $LOAEL_{HEC}$ = Human Equivalent Concentration of the LOAEL (lowest-observed-adverse effect level) $RDDR_{TH}$ = Regional Deposited Dose Ratio for Respiratory Effects in the Thoracic Region Thus, the proposed intermediate inhalation MRL is derived as follows:	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 Mean Relative Lung to Body Weights for Male Rats Exposed to $TiCl_4$ 6 hrs/day for 20 days Group / 0 post-exp days / 13 post-exp days / 84 post-exp days / 181 post-exp days Controls 0.5015 0.5066 0.4266 0.3392 5.0 mg/m^3 0.6305* 0.5159 0.4479 0.4080 10.0 mg/m^3 0.6820* 0.5753* 0.4749 0.4110 40.0 mg/m^3 0.8914* 0.6494* 0.4908 0.4713* *significant at <0.05 Results: • Respiratory Tract Infection – Showed dose-dependent acute inflammation of the respiratory tract at the end of the 4-wk period in intermediate and highest exposure levels; after 2-wk recovery, inflammation had subsided • Lung-to-Body Weight Ratio – elevated in all exposed groups on the last exposure group and in mid- and high-exposure groups after 2 weeks. Returned to normal at 3 months post-exposure **Conclusion**: Most significant findings were partial obstruction to

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
MRL = $LOAEL_{HEC}$ ÷ UF MRL = 1.032 mg/m^3 ÷ 90 MRL = 0.01 mg/m^3	the tracheal lumen with precipitated dust particles, denuded tracheal epithelium, acute obliterative bronchiolitis, interstitial pneumonitis, pulmonary edema, and hemorrhage. Results from pathological examination showed that rats in the low-exposure group, sacrificed up to one year after exposure, had only a mild lung dust cell reaction. The mid- and high-exposure groups showed a concentration-dependent inflammation of the respiratory tract. Alterations consisted of acute bronchiolitis, interstitial pneumonitis, proliferation of alveolar cells, and hyperplasia of the tracheal epithelium with hypermucous secretion. These lesions gradually disappeared after recovery and dust cells became sharply focalized. Collagenized fibrosis in the bronchioles and adjoining alveolar walls persisted throughout the 12-months recovery period. Relative lung weight was significantly elevated in all treated groups on the last exposure day and on the mid-and high-exposure groups 2 weeks post-exposure. Lung weight returned to normal 3 months post-exposure.

Table 1 – Summary table – Inhalation

Reference, design	Results
EPA 1986 **Species/Strain/Sex:** Rat/Crl-CD/Male & Female **N =** 800; 100 males & 100 females at each dose level **Exposure**: Inhalation Exposure 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10 mg/m3; **Endpoint:** Respiratory pathology ****Information used to derive Minimal Risk Level (MRL) for Inhalation Chronic Exposure** Dose and end point used for MRL derivation: The 0.1 mg/m^3 is considered a less serious LOAEL for increased incidence of rhinitis and tracheitis. Uncertainty Factors used in MRL derivation: 3 for use of a minimal LOAEL 3 for extrapolation from animals to humans 10 for human variability $LOAEL_{HEC} = LOAEL \times RDDR_{ET}$ $= 0.1 \times 0.1201$ $= 0.01201\ mg/m^3$ where: $LOAEL_{HEC}$ = Human Equivalent concentration of the LOAEL (lowest-observed-adverse effect level) $RDDR_{ET}$ = Regional Deposited Dose Ratio for Respiratory Effect in the Extrathoracic Region Thus, the proposed chronic inhalation MRL was derived as follows: $MRL = LOAEL_{HEC} \div UF$ $MRL = 0.01201\ mg/m^3 \div 90$ $MRL = 0.0001\ mg/m^3$	Exposure Level / Mean (mg/m3) / Variance / Effects Controls: 0 / 0 Low: 0.1 / 0.02 — incidence of rhinitis increased over controls; lungs maintained normal architecture; few dust cells were found in alveoli, but there were no tissue responses Medium: 1.0 / 0.10 — increased incidence of rhinitis and tracheitis; small dust aggregates were found High: 10.1 / 0.6 — Increased incidence of rhinitis and tracheitis; compound-related pathological lesions included a dust cell response with Type II pneumocyte hyperplasia, foamy macrophage infiltration, cholesterol granulomas, alveolar proteinosis, and alveolar bronchiolarization Irregular Respiration/Lung Noise Dose (mg/m3) / Sex / N outcome/N total 0 / Males / 8/100 0 / Females / 8/100 0.1 / Males / 12/100 0.1 / Females / 16/100 1.0 / Males / 24/100 1.0 / Females / 44/100 10.0 / Males / 36/100 10.0 / Females / 41/100 **Conclusions:** Mean absolute and relative lung weights in high exposure in both sexes were significantly greater than controls at 1 and 2-yr sacrifices. Pleural surface of the lungs showed an increased number and size of yellow hydrolysis product laden foci at the high exposure level. Tracheobronchial lymph nodes were slightly enlarged and mottled with yellow $TiCl_4$ hydrolysis product laden foci in intermediate and high exposure groups. Exposure resulted in dose-related transmigration of dust particles from lung through lymphatic to tracheobronchial lymph nodes, liver and spleen - none of these resulted in significant tissue responses.
Lee et al. 1986 **Species/Strain/Sex:** Rat/Crl:CD /Male & Female **Exposure:** inhalation exposure; 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10.0 mg/m^3 **Endpoint:** Respiratory pathology	

Table 1 – Summary table – Inhalation

Reference, design	Results
****Information used to derive Minimal Risk Level (MRL) for Inhalation Chronic Exposure** Dose and end point used for MRL derivation: The 0.1 mg/m^3 is considered a less serious LOAEL for increased incidence of rhinitis and tracheitis. Uncertainty Factors used in MRL derivation: 3 for use of a minimal LOAEL 3 for extrapolation from animals to humans 10 for human variability $LOAEL_{HEC} = LOAEL \times RDDR_{ET}$ $= 0.1 \times 0.1201$ $= 0.01201$ mg/m^3 where: $LOAEL_{HEC}$ = Human Equivalent concentration of the LOAEL (lowest-observed-adverse effect level) $RDDR_{ET}$ = Regional Deposited Dose Ratio for Respiratory Effect in the Extrathoracic Region Thus, the proposed chronic inhalation MRL was derived as follows: $MRL = LOAEL_{HEC} \div UF$ $MRL = 0.01201$ mg/m^3 $\div 90$ MRL =0.0001 mg/m^3	Nasal Cavity – Rhinitis, anterior Dose / Sex / N outcome/ N total 0 Male 25/79 0 Female 18/76 0.1 Male 47/73 0.1 Female 46/73 1.0 Male 41/73 1.0 Female 33/77 10.0 Male 48/73 10.0 Female 38/69 Nasal Cavity – Rhinitis, posterior Dose / Sex / N outcome/ N total 0 Male 13/79 0 Female 3/76 0.1 Male 23/73 0.1 Female 16/73 1.0 Male 22/73 1.0 Female 13/77 10.0 Male 22/73 10.0 Female 16/69 Trachea – Tracheitis, chronic Dose / Sex / N outcome/ N total 0 Male 2/79 0 Female 0/77 0.1 Male 8/67 0.1 Female 13/69 1.0 Male 35/72 1.0 Female 29/70 10.0 Male 31/71 10.0 Female 21/69 Lung – Foamy Macrophage Infiltration Dose / Sex / N outcome/ N total 0 Male 14/79 0 Female 8/77 0.1 Male 8/77 0.1 Female 3/75 1.0 Male 10/77 1.0 Female 13/78 10.0 Male 49/69 10.0 Female 61/74 Lung – Alveolar cell Hyperplasia, TiCl4 dust Dose / Sex / N outcome/ N total 0 Male 0/79 0 Female 0/77 0.1 Male 0/77 0.1 Female 0/75 1.0 Male 49/77 1.0 Female 25/78 10.0 Male 69/69 10.0 Female 73/74

Table 1 – Summary table – Inhalation

Reference, design	Results
	Lung – Bronchiolarization, alveoli Dose / Sex / N outcome/ N total 0 / Male / 1/79 0 / Female / 1/77 0.1 / Male / 0/77 0.1 / Female / 0/75 1.0 / Male / 0/77 1.0 / Female / 1/78 10.0 / Male / 15/69 10.0 / Female / 7/74 Lung – Squamous Cell Carcinoma, differentiated Dose / Sex / N outcome/ N total 0 / Male / 0/79 0 / Female / 0/77 0.1 / Male / 0/77 0.1 / Female / 0/75 1.0 / Male / 0/77 1.0 / Female / 0/78 10.0 / Male / 2/69 10.0 / Female / 3/74 **Conclusion**: No abnormal clinical signs, body weight changes, or mortality in any exposed groups. No pathological changes other than mild rhinitis and tracheitis were observed. In the lungs, pathological signs of chronic tissue response, such as macrophage reaction and alveolar cell hyperplasia, were observed. Presence of carcinoma was found at the highest dose of exposure. However, later pathological reexamination of the cancer lesions concluded that 3 of the lesions should have been diagnosed as squamous metaplasia and the other two as proliferative keratin cysts (DuPont 1994)

Cardiovascular Effects:

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Cardiovascular histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • No histopathological alterations were reported in the heart and aorta

Gastrointestinal Effects:

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Gastrointestinal pathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • No compound-related alterations were observed in the esophagus, stomach, duodenum, jejunum, cecum, and colon

Hematological Effects:

Table 1 – Summary table – Inhalation

Reference, design	Results
Lawson 1961 (United States) **Human Study** **Study Design:** Cohort **N** = 10 **Exposure:** Occupational – Chronic **Study Summary:** Plant workers with 4+ year's exposure to fumes **Endpoint:** Hematologic biochemistry	**Results:** • No abnormal values for hemoglobin, white blood cells, neutrophils, monocytes, and basophils were found in 10 worker exposed for 4-17 years to low levels of fumes • Three of the workers had mild eosinophilia • Four had relative lymphocytosis

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3 **Endpoint:** Hematologic biochemistry	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** No significant hematological alterations were reported – looked at red cell count, total and differential white cell count, hemoglobin, hematocrit, mean cell volume, and mean corpuscular hemoglobin concentration
EPA 1986 **Species/Strain/Sex:** Rat/Crl-CD/Male & Female **N** = 800; 100 males & 100 females at each dose level **Exposure**: Inhalation Exposure 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10 mg/m^3 **Endpoint:** Hematologic biochemistry	**Conclusions:** Males and females at the highest exposure had a statistically significant increase in neutrophils and a decrease in lymphocytes. High-dose males had significant decrease in erythrocytes and increases in mean cell volume and mean cell hemoglobin.
Lee et al. 1986 **Species/Strain/Sex**: Rat/Crl:CD/Male & Female **Exposure:** inhalation exposure; 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10.0 mg/m^3 **Endpoint:** Hematologic biochemistry	**Conclusion:** Males and females at the highest exposure had a statistically significant increase in neutrophils and a decrease in lymphocytes. High-dose males had significant decrease in erythrocytes and increases in mean cell volume and mean cell hemoglobin.

Hepatic Effects:

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N** = 100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Hepatic histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • No histopathological effects were observed in the liver

Renal Effects:

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3 **Endpoint:** Renal biochemistry	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • Urine Analysis – Exposure to $TiCl_4$ resulted in lower plasma urea nitrogen, urine osmolality and higher urine pH of rats after the exposure to intermediate and highest levels. 14 days later, these were in the normal range established by controls

Endocrine Effects:

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Endocrine histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • No compound-related histopathological alterations were observed in the thyroid, parathyroid and pancreas

Dermal Effects:

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Skin histopathology	<table><tr><th>Exposure Level</th><th>N</th><th>Mean (mg/m^3)</th><th>Standard Deviation</th></tr><tr><td>Controls</td><td>25</td><td>0</td><td>0</td></tr><tr><td>Low</td><td>25</td><td>4.9</td><td>0.9</td></tr><tr><td>Intermediate</td><td>25</td><td>10</td><td>1.9</td></tr><tr><td>High</td><td>25</td><td>40</td><td>5.9</td></tr></table> **Results:** • No histopathological alterations were observed in the skin

Ocular Effects:

Table 1 – Summary table – Inhalation	
Reference, design	**Results**
Ross 1985 **Human Study** **Study Design:** Case Report **N** = 3 **Exposure:** Occupational – Acute **Study Summary:** Research workers were using $TiCl_4$ to assess a welding torch. Brass tap flew off filling the room with fumes **Endpoint:** Ocular function	One worker complained of eye irritation for 2 hours post exposure. Upon medical examination several hours later, no abnormalities were found.
Park et al. 1984 (United States) **Human Study** **Study Design:** Case Report **Exposure**: Occupational – Acute **Study Summary:** 50-yr old chemical engineer was admitted to the ICU in respiratory failure after industrial accident. Exposed for about 2 minutes to the vapor from a cloud that had formed when $TiCl_4$ was exposed to the air **Endpoint:** Ocular pathology	The patient developed delayed complications from inhalation of products produced from the hydrolysis of $TiCl_4$. Upon removing his mask, his eyes were exposed to the vapors. No information was given about the dose or the course of his eye injury.
Karlsson et al. 1986 **Species/Strain/Sex:** Rat/Sprague-Dawley/Female **N** = 12; 3 juvenile rats/exposure concentration **Exposure:** Inhalation Exposure, single exposure to 1466, 5112, 7529, and 11492 mg/m3 for 10 minutes. **Study Summary:** • Acute inhalation of pure $TiCl_4$ – 10-minute exposure at different concentrations of Ti	Preliminary Experiment: no deaths at any concentration of TiO_2-HC smoke mixture 10-minute exposure: Animals exposed to the highest concentrations showed wet noses, nasal discharge and swollen eyelids; most animals appeared normal 24-48 hours after exposure. **Conclusion**: All animals at the different levels showed marked

Table 1 – Summary table – Inhalation

Reference, design	Results
Endpoint: Ocular pathology	signs of irritation; all animals showed an essentially normal lung picture after 7 days
DuPont 1980 **Species/Strain/Sex:** Rat/Crl-CD/Male **N=** 24; 6 rats/group, 4 groups/exposure time **Exposure:** Inhalation Exposure, head only, single exposure; 460 – 108,000 mg/m^3 for 2-240 minutes. **Endpoint:** Nonneoplastic eye lesions	**Results/Conclusions:** Corneal opacity, necrotic keratitis, and conjunctivitis were reported in rats exposed to lethal concentrations of titanium tetrachloride for 2-240 minutes.
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3 **Endpoint:** Ocular histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results:** • No histopathological alterations were observed in the eyes

Body Weight Effects:

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1980 **Species/Strain/Sex:** Rat/Crl-CD/Male **N=** 24; 6 rats/group, 4 groups/exposure time **Exposure:** Inhalation Exposure, head only, single exposure; 460 – 108,000 mg/m^3 for 2-240 minutes. **Endpoint:** Body weight	**Result/Conclusions:** Surviving rats exposed to median lethal concentrations of titanium tetrachloride hydrolysis products for 2-240 minutes exhibited weight loss (unquantified) after exposure
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3 **Endpoint:** Body weight	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results**/Conclusion: • Body Weight – highest exposure group showed labored respiration and a 19% reduction in weight-gain. Returned to normal after recovery. Other exposure groups were similar to controls
EPA 1986 **Species/Strain/Sex:** Rat/Crl-CD/Male & Female **N =** 800; 100 males & 100 females at each dose level **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10 mg/m^3 **Endpoint:** Body weight	**Result/Conclusions:** Overall, mean body weight gains varied slightly in the 1.0 and 10.0 mg/m^3 dose levels for both sexes when compared to their respective controls
Lee et al. 1986 **Species/Strain/Sex**: Rat/Crl:CD/Male & Female **Exposure:** inhalation exposure; 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10.0 mg/m^3 **Endpoint:** Body weight	**Result/Conclusion**: No abnormal clinical signs, body weight changes, or mortality in any exposed groups.

2.2.1.3 Immunological and Lymphoreticular Effects

No new data were identified with regards to inhalation exposure to titanium tetrachloride and immunological and lymphoreticular effects.

See below for studies previously evaluated.

Table 1 – Summary table – Inhalation

Reference, design	Results
Park et al. 1984 (United States) **Human Study** **Study Design:** Case Report **Exposure**: Occupational – Acute **Study Summary:** 50-yr old chemical engineer was admitted to the ICU in respiratory failure after industrial accident. Exposed for about 2 minutes to the vapor from a cloud that had formed when $TiCl_4$ was exposed to the air **Endpoint:** Hematologic biochemistry	**Result/Conclusion:** The patient developed delayed complications from inhalation of products produced from the hydrolysis of $TiCl_4$. Found an elevated lymphocyte count of 23,700 cells/mm^3. No other information or details of exposure were provided.
Lawson 1961 (United States) **Human Study** **Study Design:** Cohort **N** = 10 **Exposure:** Occupational – Chronic **Study Summary:** Plant workers with 4+ year's exposure to fumes **Endpoint:** Hematologic biochemistry	**Result/Conclusion:** found relative lymphocytosis in 4 of the exposed workers
Redline et al. 1986 (United States) **Human Study** **Study Design:** Case Report **Exposure:** Occupational – Chronic (13 years) **Study Summary:** A 45 year old black man had been well until five years previously (1978) when he noted progressive dyspnea associated with a non-productive cough. Respiratory symptoms, which initially occurred only at work, were subsequently experienced throughout the day. He had no known exposure to individuals with tuberculosis and had no other medical problems. **Endpoint:** Cellular immune function	A patient presented with granulomatous lung disease associated with the pulmonary deposition of various metallic particles **Result/Conclusions:** found impaired cellular immune function
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N**=100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Hematologic biochemistry	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 **Results/Conclusion**: • No histopathological alterations were observed in the thymus and spleen. No further immunological parameters were evaluated
EPA 1986 **Species/Strain/Sex:** Rat/Crl-CD/Male & Female **N** = 800; 100 males & 100 females at each dose level **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10 mg/m^3 **Endpoint:** Hematologic biochemistry	**Results/Conclusions:** High-dose males had significant decrease in erythrocytes and increases in mean cell volume and mean cell hemoglobin. The incidence of macrophage containing small amount of particles (foamy dust macrophages) was increased in rats receiving 10.0 mg/m^3 of hydrolyzed titanium tetrachloride. Dose-related changes observed in the tracheobronchial lymph nodes of rats exposed to 1.0 and 10.0 mg/m^3 included slight

Table 1 – Summary table – Inhalation

Reference, design	Results
	enlargement of the nodes and foci laden with yellow titanium tetrachloride hydrolysis product. . Exposure resulted in dose-related transmigration of dust particles from lung through lymphatic to tracheobronchial lymph nodes, liver and spleen - none of these resulted in significant tissue responses.
Lee et al. 1986 **Species/Strain/Sex**: Rat/Crl:CD/Male & Female **Exposure:** inhalation exposure; 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10.0 mg/m^3 **Endpoint:** Macrophage Infiltration	Lung – Foamy Macrophage Infiltration Dose / Sex / N outcome/ N total 0 / Male / 14/79 0 / Female / 8/77 0.1 / Male / 8/77 0.1 / Female / 3/75 1.0 / Male / 10/77 1.0 / Female / 13/78 10.0 / Male / 49/69 10.0 / Female / 61/74 Lung – Alveolar cell Hyperplasia, TiCl4 dust Dose / Sex / N outcome/ N total 0 / Male / 0/79 0 / Female / 0/77 0.1 / Male / 0/77 0.1 / Female / 0/75 1.0 / Male / 49/77 1.0 / Female / 25/78 10.0 / Male / 69/69 10.0 / Female / 73/74 Lung – Bronchiolarization, alveoli Dose / Sex / N outcome/ N total 0 / Male / 1/79 0 / Female / 1/77 0.1 / Male / 0/77 0.1 / Female / 0/75 1.0 / Male / 0/77 1.0 / Female / 1/78 10.0 / Male / 15/69 10.0 / Female / 7/74 **Conclusion**: In the lungs, pathological signs of chronic tissue response, such as macrophage reaction and alveolar cell hyperplasia, were observed.

2.2.1.4 Neurological Effects

No new data were identified with regards to inhalation exposure to titanium tetrachloride and neurological effects.

See below for studies previously evaluated.

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Neurological histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 Results: • No histopathological alterations were observed in the brain

2.2.1.5 Reproductive Effects

No new data were identified with regards to inhalation exposure to titanium tetrachloride and reproductive effects.

See below for studies previously evaluated.

Table 1 – Summary table – Inhalation

Reference, design	Results
DuPont 1979 **Species/Strain/Sex:** Rat/Charles River-CD/Male **N=**100; 25 rats/group/control **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 4 weeks to 0, 5, 40 mg/m3. **Endpoint:** Male reproductive system histopathology	Exposure Level / N / Mean (mg/m^3) / Standard Deviation Controls 25 0 0 Low 25 4.9 0.9 Intermediate 25 10 1.9 High 25 40 5.9 Results: • No histopathological alterations were observed in the testis and epididymis

2.2.1.8 Cancer Effects

No new data were identified with regards to inhalation exposure to titanium tetrachloride and cancer.

See below for studies previously evaluated.

Table 1 – Summary table – Inhalation

Reference, Design	Results
EPA 1990b (United States) **Human Study** **Study Design:** Nested case-control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day to over 5 years **Study Summary:** Study examined incidence of and mortality (between 1935-1983) from lung cancer in workers exposed to titanium tetrachloride ($TiCl_4$); controls are population-based **Endpoint:** Lung Cancer **Reanalysis of data from Chen & Fayerweather cohort	Outcome: Lung Cancer Exposure Level: Control; N per group: 96; aOR (90% CI): Ref Exposure Level: Case; N per group: 24; aOR (90% CI): 1.1 (0.4, 3.2) Adjusted for age, smoking status, year of hire, pay class, and geographic location **Conclusions:** Lung cancer rates were not statistically significant with respect to occupational $TiCl_4$ exposure
Fayerweather et al. 1992 (United States) **Human Study** **Study Design:** Nested Case-Control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day – over 5 years. **Study Summary:** A total of 2477 employees from two titanium dioxide plants were studied. Of that group, 969 employees exposed to titanium tetrachloride were observed from 1956 through 1985 for cancer and chronic respiratory disease incidence **Endpoint:** Lung Cancer	Outcome: Lung Cancer Exposure Level (mg/m3): Referent (0); N per group: 79; aOR (90% CI): Ref Exposure Level (mg/m3): High (>3.0); N per group: 20; aOR (90% CI): 1.2 (0.3, 4.0) Adjusted for age, smoking status, employment history and Titanium Dioxide **Conclusion:** Nested case-control analyses found no statistically significant association between titanium tetrachloride exposure and risk of lung cancer, chronic respiratory disease, and chest roentgenogram abnormalities. No cases of pulmonary fibrosis were observed among titanium tetrachloride-exposed employees. Smoking was found to be a strong predictor of lung cancer mortality in the non-exposed employees with an increased risk of dying from lung cancer up to 7-fold higher in current smokers than in nonsmokers.
EPA 1984 **Species/Strain/Sex:** Rat/Charles River-CD/Male & Female **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week to 0, 0.1, 1.0, 10 mg/m^3 **Endpoint:** Lung cancer (squamous cell carcinoma)	Preliminary Results for 2-year inhalation study **Conclusion:** Sacrificed from each exposure group at 3, 6, 12, 24 months- all major tissues and organs were normal except for respiratory tract. At 24 months, exam revealed keratinized, cystic squamous cell carcinoma tumors at 10mg/m^3 exposure level
Lee et al. 1986 **Species/Strain/Sex**: Rat/Crl:CD/Male & Female **Exposure:** inhalation exposure; 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10.0 mg/m^3 **Endpoint:** Lung cancer (squamous cell carcinoma)	Lung – Squamous Cell Carcinoma, differentiated Dose: 0; Sex: Male; N outcome/ N total: 0/79 Dose: 0; Sex: Female; N outcome/ N total: 0/77 Dose: 0.1; Sex: Male; N outcome/ N total: 0/77 Dose: 0.1; Sex: Female; N outcome/ N total: 0/75 Dose: 1.0; Sex: Male; N outcome/ N total: 0/77 Dose: 1.0; Sex: Female; N outcome/ N total: 0/78 Dose: 10.0; Sex: Male; N outcome/ N total: 2/69 Dose: 10.0; Sex: Female; N outcome/ N total: 3/74 **Conclusion**: Presence of carcinoma was found at the highest dose of exposure. **However, later pathological reexamination of the cancer lesions concluded that 3 of the lesions should have been**

	diagnosed as squamous metaplasia and the other two as proliferative keratin cysts (DuPont 1994)
EPA 1986 **Species/Strain/Sex:** Rat/Crl-CD/Male & Female **N =** 800; 100 males & 100 females at each dose level **Exposure:** Inhalation Exposure 6 hours/day, 5 days/week for 2 years to 0, 0.1, 1.0, 10 mg/m^3 **Endpoint:** Cystic keratinizing squamous cell carcinomas	**Conclusions:** Cystic keratinizing squamous cell carcinomas were observed primarily in rats exposed to 10.0 mg/m^3 and the incidence was similar for male and female rats

2.2.3 Dermal Exposure

2.2.3.1 Death

No new data were identified with regards to dermal exposure to titanium tetrachloride and death.

See below for studies previously evaluated.

Table 2 – Summary table – Dermal

Reference, design	Results
Chitkara and McNeela 1992 (United Kingdom) **Human Study:** **Study Design:** Case Report **Exposure**: Occupational – Acute **Study Summary:** Case of $TiCl_4$ burns to the eye, which have been seen in our casualty department over the past 4 years, four of which illustrate this compound's propensity for severe tissue damage	Patient 8 (Male, Unknown Age) – Whole body Splash; Extensive burns to facial skin, nasopharynx and larynx; Corneas thick and opaque and extensive swelling of bulbar conjunctiva and episclera; some clearing of corneal opacification in right eye after 14 days, but not in left; severe injury to lungs by inhalation; progressive deterioration in pulmonary compliance; died 2 weeks after injury
EPA 1990b (United States) **Human Study** **Study Design:** Nested case-control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day to over 5 years **Study Summary:** Study examined incidence of and mortality (between 1935-1983) from lung cancer in workers exposed to titanium tetrachloride ($TiCl_4$); controls are population-based **Reanalysis of data from Chen & Fayerweather cohort	**Results/Conclusions**: No increase in mortality from any cause was reported in workers occupationally exposed to titanium tetrachloride.
Fayerweather et al. 1992 (United States) **Human Study** **Study Design:** Nested Case-Control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day – over 5 years. **Study Summary:** A total of 2477 employees from two titanium dioxide plants were studied. Of that group, 969 employees exposed to titanium tetrachloride were observed from 1956 through 1985 for cancer and chronic respiratory disease incidence	**Results/Conclusion:** No increase in mortality from any cause was reported in workers occupationally exposed 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

Respiratory Effects:

No new data were identified with regards to dermal exposure to titanium tetrachloride and respiratory effects.

See below for studies previously evaluated.

Table 2 – Summary table – Dermal

Reference, Design	Results
Redline et al. 1986 (United States) **Human Study** **Study Design:** Case Report **Exposure:** Occupational – Chronic (13 years) **Study Summary:** A 45 year old black man had been well until five years previously (1978) when he noted progressive dyspnea associated with a non-productive cough. Respiratory symptoms, which initially occurred only at work, were subsequently experienced throughout the day. He had no known exposure to individuals with tuberculosis and had no other medical problems. **Endpoint:** Respiratory pathology	A patient presented with granulomatous lung disease associated with the pulmonary deposition of various metallic particles **Conclusions:** chest radiograph-diffuse bilateral fibronodular infiltrates. Transbronchial biopsy from right lower lobe showed multiple non-caseating granulomas containing numerous birefirengent crystals.
Ross 1985 **Human Study** **Study Design:** Case Report **N =** 3 **Exposure:** Occupational – Acute **Study Summary:** Research workers were using $TiCl_4$ to assess a welding torch. Brass tap flew off filling the room with fumes **Endpoint:** Respiratory biochemistry	One worker complained of ticklish cough accompanied by unpleasant taste. Another developed cough and felt tightness in chest, along with eye irritation for 2 hours post exposure. Third worker experience no symptoms. None were severe, medical examination several hours later revealed no abnormalities. There were skin lesions and marked congestion of mucous membranes of pharynx, vocal cords and trachea; lesions healed with scarring

Dermal Effects:

There has been one new case report since the initial Toxicological Profile on Titanium Tetrachloride was released in 1997 pertaining to the dermal effects of the chemical after dermal exposure.

A case report looking at two hospital patients who were accidentally sprayed with liquid $TiCl_4$ reported that the compound reacted with the perspiration on their bodies and created heat and HCl vapors (Paulsen et al. 1998). The two patients had burns covering 18% and 20% of their bodies; wound repair of the burns proceeded in a predictable and timely fashion with no evidence that $TiCl_4$ persists in the wound bed after initial exposure.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
Paulsen et al. 1998 (United States; Tennessee) **Human Study** **Study Design:** Case Report **N** = 2 **Exposure**: Occupational – Acute **Study Summary:** Two hospital patients were studied after being accidentally sprayed with liquid $TiCl_4$; the compound reacted with the perspiration on their bodies and created heat and HCl vapors **Endpoint**: Skin burns	Patient 1 (Male, 28-yrs old) – Burns of 18% total body surface area Patient 2 (Male, 35-yrs old) – Burns of 20% total body surface area **Conclusion:** Wound repair of burns caused by exposure to $TiCl_4$ proceeds in a predictable and timely fashion; no evidence that $TiCl_4$ persists in the wound bed or continues to harm the skin after the initial exposure

Additionally, see below for studies previously evaluated.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
Chitkara and McNeela 1992 (United Kingdom) **Human Study** **Study Design:** Case Report **N** = 8 **Exposure**: Occupational – Acute **Study Summary:** Cases of $TiCl_4$ burns to the eye, which have been seen in our casualty department over the past 4 years, four of which illustrate this compound's propensity for severe tissue damage **Endpoint:** Skin burns	Patient 1 (Male, 20-yrs old) – Splashed $TiCl_4$ in his left eye; vision was reduced to 6/36+1 and there were mild corneal and inferior conjunctival epithelial defects in his left eye. He made an uneventful and complete recovery and was discharged 2 days later Patient 2 (Male, 39-yrs-old) – Sprayed on his face from high pressure pipe; Fortunately he was wearing goggles and only suffered Thoft grade I burns to both eyes. He made an uneventful recovery within 3 days. He also suffered severe burns to both his calves and face, requiring split skin grafts. Patient 3 (Male, 19-yrs old) – Splashed small amount onto both eyes; He suffered mild corneal punctate stains which recovered completely and uneventfully within 2 days Patient 4 (Male, 46-yrs old) – Sprayed from high pressure pipe; He suffered Thoft grade 4 corneal and conjunctival burns, especially in the right eye. Left eye healed rapidly within 3 days. Right eye subsequently developed a sterile hypopyon and raised intraocular pressure. This resolved slowly over a 17 day period. A small corneal epithelial defect remained. Healing was complicated by entropion and trichiasis; corneal scarring and vascularization over a 6 week period. Eye became totally blind and painful within 2 years.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
	Patient 5 (Male, 42-yrs old) – Sprayed liquid into both eyes; Left eye - Thoft 1 grade burns, settled in 3 days. Right eye- Thoft 4 grade corneal and conjunctival burns with conjunctival ischemia and anterior uveitis; progressed to right corneal perforation; right eye became blind and irritable and was later enucleated Patient 6 (Male, 42-yrs old) – Sprayed liquid into both eyes and face; Right eye affected more severely. On presentation there was a large central corneal epithelial defect together with stromal oedema. Severe chemosis and ischemia. Eye settled slowly and patient developed corneal vascularization and cicatrical changes within 3-4 weeks. 6 months- symblepharon formation. Had multiple corneal surgeries to try and heal Patient 7 (Male, 21-yrs old) – accidental splash in right eye; Thoft grade 2 chemical burn; defects of inferior corneal and conjunctival epithelium; next 6 months-persistent vascular engorgement of the conjunctiva; suffered no permanent visual loss; 2-yr follow-up -> no significant abnormality Patient 8 (Male, Unknown Age) – Whole body Splash; Extensive burns to facial skin, nasopharynx and larynx; Corneas thick and opaque and extensive swelling of bulbar conjunctiva and episclera; some clearing of corneal opacification in right eye after 14 days, but not in left; severe injury to lungs by inhalation; progressive deterioration in pulmonary compliance; died 2 weeks after injury
Lawson 1961 (United States) **Human Study** **Study Design:** Case Report **N** = 4 **Exposure:** Occupational – Acute **Endpoint:** Skin burns	Patient 1 (Male, 35-yrs old) – sprayed with large quantity of liquid $TiCl_4$; 3rd-degree burns on feet, abdomen, lumbar, pilonidal, perirectal and pubic areas Patient 2 (Male, 43-yrs old) – sprayed with liquid $TiCl_4$; 3rd-degree burns to his hand Patient 3 (Male, 50-yrs old) – drenched from waist down in ordinary clothes; 3rd-degree burn on his ankle Patient 4 – 0.5cc purified anhydrous $TiCl_4$-left 1 min and wiped without water; tenacious light yellow to white granular deposit remained; onset of stinging sensation between 5-32 seconds; stinging and deposit disappeared immediately after washing with cold water

Ocular Effects

No new data were identified with regards to dermal exposure to titanium tetrachloride and ocular effects.

See below for studies previously evaluated.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
Chitkara and McNeela 1992 (United Kingdom) **Human Study** **Study Design:** Case Report **N =** 80 **Exposure**: Occupational – Acute **Study Summary:** Cases of $TiCl_4$ burns to the eye, which have been seen in our casualty department over the past 4 years, four of which illustrate this compound's propensity for severe tissue damage. **Endpoint:** Ocular burns	Patient 1 (Male, 20-yrs old) – Splashed $TiCl_4$ in his left eye; vision was reduced to 6/36+1 and there were mild corneal and inferior conjunctival epithelial defects in his left eye. He made an uneventful and complete recovery and was discharged 2 days later Patient 2 (Male, 39-yrs-old) – Sprayed on his face from high pressure pipe; Fortunately he was wearing goggles and only suffered Thoft grade I burns to both eyes. He made an uneventful recovery within 3 days. He also suffered severe burns to both his calves and face, requiring split skin grafts. Patient 3 (Male, 19-yrs old) – Splashed small amount onto both eyes; He suffered mild corneal punctate stains which recovered completely and uneventfully within 2 days Patient 4 (Male, 46-yrs old) – Sprayed from high pressure pipe; He suffered Thoft grade 4 corneal and conjunctival burns, especially in the right eye. Left eye healed rapidly within 3 days. Right eye subsequently developed a sterile hypopyon and raised intraocular pressure. This resolved slowly over a 17 day period. A small corneal epithelial defect remained. Healing was complicated by entropion and trichiasis; corneal scarring and vascularization over a 6 week period. Eye became totally blind and painful within 2 years. Patient 5 (Male, 42-yrs old) – Sprayed liquid into both eyes; Left eye - Thoft 1 grade burns, settled in 3 days. Right eye- Thoft 4 grade corneal and conjunctival burns with conjunctival ischemia and anterior uveitis; progressed to right corneal perforation; right eye became blind and irritable and was later enucleated Patient 6 (Male, 42-yrs old) – Sprayed liquid into both eyes and face; Right eye affected more severely. On presentation there was a large central corneal epithelial defect together with stromal oedema. Severe chemosis and ischemia. Eye settled slowly and patient developed corneal vascularization and cicatrical changes within 3-4 weeks. 6 months- symblepharon formation. Had multiple corneal surgeries to try and heal Patient 7 (Male, 21-yrs old) – accidental splash in right eye; Thoft grade 2 chemical burn; defects of inferior corneal and conjunctival epithelium; next 6 months-persistent vascular engorgement of the conjunctiva; suffered no permanent visual loss; 2-yr follow-up -> no significant abnormality Patient 8 (Male, Unknown Age) – Whole body Splash; Extensive burns to facial skin, nasopharynx and larynx; Corneas thick and opaque and extensive swelling of bulbar conjunctiva and episclera; some clearing of corneal opacification in right eye after 14 days, but not in left; severe injury to lungs by inhalation; progressive deterioration in pulmonary compliance; died 2 weeks after injury

2.2.3.3 Immunological and Lymphoreticular Effects

No new data were identified with regards to dermal exposure to titanium tetrachloride and immunological and lymphoreticular effects.

See below for studies previously evaluated.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
Redline et al. 1986 (United States) **Human Study** **Study Design:** Case Report **Exposure:** Occupational – Chronic (13 years) **Study Summary:** A 45 year old black man had been well until five years previously (1978) when he noted progressive dyspnea associated with a non-productive cough. Respiratory symptoms, which initially occurred only at work, were subsequently experienced throughout the day. He had no known exposure to individuals with tuberculosis and had no other medical problems. **Endpoint:** Cellular immune function	A patient presented with granulomatous lung disease associated with the pulmonary deposition of various metallic particles Conclusions: chest radiograph-diffuse bilateral fibronodular infiltrates. transbronchial biopsy from right lower lobe showed multiple non-caseating granulomas containing numerous birefirengent crystals.

2.2.3.8 Cancer Effects

No new data were identified with regards to dermal exposure to titanium tetrachloride and cancer.

See below for studies previously evaluated.

Table 2 – Summary table – Dermal	
Reference, Design	**Results**
EPA 1990b (United States) **Human Study** **Study Design:** Nested case-control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day to over 5 years **Study Summary:** Study examined incidence of and mortality (between 1935-1983) from lung cancer in workers exposed to titanium tetrachloride ($TiCl_4$); controls are population-based **Endpoint:** Lung cancer **Reanalysis of data from Chen & Fayerweather cohort	Outcome / Exposure Level / N per group / aOR (90% CI) Lung Cancer / Control / 96 / Ref Lung Cancer / Case / 24 / 1.1 (0.4, 3.2) Adjusted for age, smoking status, year of hire, pay class, and geographic location **Conclusions:** Lung cancer rates were not statistically significant with respect to occupational $TiCl_4$ exposure
Fayerweather et al. 1992 (United States) **Human Study** **Study Design:** Nested Case-Control **N** = 120 adult males; cases – N=24; controls – N=96 **Exposure:** Occupational; 1 day – over 5 years.	Outcome / Exposure Level (mg/m^3) / N per group / aOR (90% CI) Lung Cancer / Referent (0) / 79 / Ref Lung Cancer / High (>3.0) / 20 / 1.2 (0.3, 4.0)

<table>
<tr><th colspan="2">Table 2 – Summary table – Dermal</th></tr>
<tr><th>Reference, Design</th><th>Results</th></tr>
<tr><td>Study Summary: A total of 2477 employees from two titanium dioxide plants were studied. Of that group, 969 employees exposed to titanium tetrachloride were observed from 1956 through 1985 for cancer and chronic respiratory disease incidence
Endpoint: Lung cancer</td><td>Adjusted for age, smoking status, employment history and Titanium Dioxide

Conclusion: Nested case-control analyses found no statistically significant association between titanium tetrachloride exposure and risk of lung cancer, chronic respiratory disease, and chest roentgenogram abnormalities. No cases of pulmonary fibrosis were observed among titanium tetrachloride-exposed employees. Smoking was found to be a strong predictor of lung cancer mortality in the non-exposed employees with an increased risk of dying from lung cancer up to 7-fold higher in current smokers than in nonsmokers.</td></tr>
<tr><td>Chen and Fayerweather 1988 (United States)

Human Study
Study Design: Retrospective Cohort
N = 1576
Exposure: Occupational
Study Summary: 1576 employees (all male employed >1yr) exposed to TiO_2 observed from 1956-1985 for cancer and chronic respiratory disease; and from 1935-1983 for mortality; cross-sectional sample of 398 employees evaluated for chest roentgenogram abnormalities
Endpoint: Lung cancer</td><td>
<table>
<tr><th>Outcome</th><th>Exposure Level (mg/m^3)</th><th>N per group</th><th>aOR (90% CI)</th></tr>
<tr><td>Lung Cancer Incidence</td><td>Referent (0)
Moderate (4-9)</td><td>898
16</td><td>Ref
0.6 (0.2, 2.2)</td></tr>
<tr><td>Lung Cancer Mortality</td><td>Referent (0)
Very High (20+)</td><td>331
27</td><td>Ref
0.3 (0.1, 1.9)</td></tr>
<tr><td>Chronic Respiratory Disease</td><td>Referent (0)
Very High (20+)</td><td>898
88</td><td>Ref
0.8 (0.3, 1.7)</td></tr>
<tr><td>Pleural Thickening & Plaques</td><td>Referent (0)
High (>9-20)</td><td>372
22</td><td>Ref
0.6 (0.1, 4.3)</td></tr>
</table>
Adjusted for age and sex

Conclusion:
• Overall observed number of cancer cases was slightly higher - 8 lung cancer cases observed compared to 7.7 expected - this was not statistically significant
• Nested case-control, based on 27 lung cancer deaths and 331 non-cancer decedent controls, showed no statistically significant association between TiO_2 exposure and lung cancer
• No association between TiO_2 exposure and pleural thickening and pleural plaques</td></tr>
</table>

2.2.4 Other Routes of Exposure – Intraperitoneal

2.2.4.6 Developmental Effects

No new data were identified with regards to dermal exposure to titanium tetrachloride and developmental effects.

See below for studies previously evaluated.

Table 3 – Summary table – Other Exposure – Intraperitoneal	
Reference, Design	**Results**
Tsujii and Hoshishima 1979 **Species/Strain/Sex**: Mice/CFW/Male & Female **Study Design:** Adult female mice were injected at 8 weeks of pregnancy. Assessment done on the offspring **Exposure:** Intra-Peritoneal injection**;** 11 injections of 0.1 mL solution **Endpoint:** Neuro-motor development	**Results:** • Geotaxis: male offspring of injected individuals showed delayed response in turning head up and significant delay in response to upward creeping • Showed significant acceleration in the straight walking test in males • Offspring of injected mice showed significant acceleration in pivoting, rooting reflex, grasp reflex, crossed extensor and auditory startle • Showed significant delay in righting reflex • Maze test- significant numbers of errors observed in female cases

2.2.5 Other Exposure – *In Vitro*

There have been two new *in vitro* studies completed since the initial Toxicological Profile on Titanium Tetrachloride was published in 1997.

Recent studies conducted using *in vitro* analyses have shown some associations with Titanium Tetrachloride. Cadosch et al. (2010) investigated the influence of titanium on the function of human t-lymphocytes. They found that titanium influences phenotype and function of T-lymphocytes, resulting in activation of a CD69+ and CCR4+ T-lymphocyte population and secretion of RANK-L. RANK-L is crucial in the activation, maturation and function of osteoclasts. Another investigation looking at titanium's effect on the number of osteoclasts and osteoblasts present in a Mouse Primary Cell Line found that the number of osteoblasts was not significantly different between the controls and the exposure group. The *in vitro* experiment showed that titanium ions caused a preferential degradation of osteoclasts rather than osteoblasts, most likely by apoptosis (Matsunaga et al. 2001).

Table 4 – Summary table – Other Exposure – *In Vitro*

Reference, design	Results
Cadosch et al. 2010 **Cell Line:** Human Primary Blood Cells (PBMC) **Endpoint:** Influence of Titanium on the function of human T-lymphocytes in vitro • RANK-L Cytokine Expression – RANK-L is crucial in activation, maturation and function of osteoclasts	Direction of Effect Dose Level / RANK-L Cytokine Expression / PHA activated T-Cell Proliferation Rate 0 / Ref / Ref 3.125 / NR / ↑ 6.25 / NR / ↑ 12.5 / ↑ / ↑ 25 / NR / ↑ 50 / ↑ / ↑ 100 / ↑ / ↔ **Conclusion:** Titanium influences phenotype and function of T-lymphocytes, resulting in activation of a CD69+ and CCR4+ T-lymphocyte population and secretion of RANK-L
Matsunaga et al. 2001 **Cell Line:** Mouse Primary osteoclast/osteoblast Cell Line (ICR) **Endpoint:** Titanium's effect on the number of osteoclasts and osteoblasts present	Outcomes / # of apoptotic cells Mean (Variance) / # of TRAP+ cells* Mean (Variance) Controls / 13.50 (0.61) / 38.37 (0.19) Cases (10µM Ti) / 15.38 (0.98) / 17.25 (0.38) *Measure of a decrease in the number of osteoclast cells **Conclusion:** The number of osteoblasts was not significantly different between the controls and the exposure group. Titanium ions caused a preferential degradation of osteoclasts rather than osteoblasts, most likely by apoptosis

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

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

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

No updated data.

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

No updated data.

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APPENDIX 1: Overview of protocol for systematic review of Titanium Tetrachloride

This appendix provides the step by step protocol implemented for this systematic review.

Eligibility criteria for considering studies for this review

Types of Studies

All human, animal and *in vitro* studies with relevant information on exposure toTitanium Tetrachloride.

Types of participants and model systems

Studies of humans, experimental animals, and from "supporting evidence" provided by *in vitro* studies.

There will be no exclusions based on lifestage at exposure or assessment or sex of the animals, or based on *in vitro* model system. Animal species and strains will be limited to mammals for the purpose of extrapolation to human outcomes and effects.

Types of Exposures

Exposure to Titanium Tetrachloride (CAS# 7550-45-0) based on administered dose or concentration, biomonitoring data (e.g. urine, blood, or other specimens), environmental measures (e.g. air, water levels), or indirect measures such as job title.

There will be no exclusions based on the analytical method used to measure Titanium Tetrachloride.

Types of Outcomes

Publications must include an indicator of Titanium Tetrachloride exposure analyzed in relation to any one of the following primary or secondary outcomes:

I. Discussion of Health Effects by Route of Exposure (Inhalation, Oral, or Dermal)
    a. Death
    b. Systemic Effects
    c. Immunological and Lymphoreticular Effects
    d. Neurological Effects
    e. Reproductive Effects
    f. Developmental Effects
    g. Genotoxic Effects
    h. Cancer
II. Toxicokinetics: Absorption, Distribution, Metabolism and Excretion

III. Relevance to Public Health
IV. Biomarkers of Exposure and Effect
V. Interactions with Other Substances
VI. Populations that are Unusually Susceptible
VII. Methods for Reducing Toxic Effects
VIII. Adequacy of the Database: Identification of data needs and ongoing studies
IX. Chemical and Physical Information
X. Production, Import/Export, Use and Disposal
XI. Potential for Human Exposure: Releases to the environment, Environmental fate, Levels monitored or estimated in the environment, General population and occupational exposure, Populations with potentially high exposures
XII. Analytical Methods: Biological Samples, Environmental Samples
XIII. Regulations and Advisories

All other studies returned from the literature search that did not pertain to one of these topics of interest in conjuncture with Titanium Tetrachloride were excluded.

Types of Publications

Publications must be peer-reviewed articles published through March 2013. There are no language restrictions.

Database Searches

The following databases were searched from inception to March 2013:

- PubMed
- Web of Knowledge

The search strategy used the CAS number for Titanium Tetrachloride (CAS# 7550-45-0) and MESH terms for the chemical.

Searching Other Resources

Hand searches were done to identify any study included in the original profile that did not come up on the original database search including technical reports from government agencies or scientific research groups.

Duplicate Citations

The results of the literature search will be downloaded into Endnote X5 software. Exact article duplicates will be removed using Endnote X5 software prior to uploading into DistillerSR®

Web-Based Systematic Review Software3. The duplicate detection feature in DistillerSR® will also be used to detect and remove duplication citations; this feature looks for similarities in articles based on author and title content. If an article is a duplicate, a member of the review team "quarantines" the article such that it is removed from the main project with an annotation for reason, although the article is not deleted and can be retrieved later if needed. Multiple publications from the same study population identified during full-text review will be evaluated for duplicate data. For studies with multiple publications on the same population, we will select the publication with the longest follow-up as the primary report for data analysis and consider the other as secondary publications. For studies with equivalent follow-up periods, we will select the study with the largest number of cases or the most recent publication as the primary report.

Screening Studies for Eligibility

We will use DistillerSR® for screening studies. Screeners will be trained using written documentation on study eligibility with an initial pilot phase undertaken to improve clarity of the inclusion and exclusion language and to improve accuracy and consistency among screeners. Articles will first be independently reviewed at the title and abstract level by two members of the review team.

Disagreements between the 2 screeners will be resolved by each screener independently reviewing the conflicts noted in DistillerSR®, modifying and discussing responses as appropriate to resolve, and arbitration by a third member of the review team if necessary. A copy of articles that appear to meet the inclusion criteria based on the title and abstract screen will be obtained for full-text review unless the article is not available after an attempt has been made to obtain it. Copies of articles that cannot be assessed for relevance based on the title and abstract screen will also be obtained to determine eligibility based on full-text review. Studies will not be considered further when the title and abstract clearly indicate that the study does not meet the inclusion criteria described above.

Full-text eligibility review will also be independently conducted by two members of the review team with reasons for exclusion annotated and tracked (e.g., "review paper with no original data"). The primary reason for excluding studies will be if the article does not contain original data relevant to our eligibility criteria. If the full text of an article is not in English, then translation services or consultation with a fluent scientist will be utilized to determine relevance for inclusion. Flow of information through the different phases of the review are documented in Figure 1.

Data Extraction and Management

We will use customized data extraction forms in DistillerSR® to collect information on study design, experimental model, methodology and results. Each team member's data extraction will be reviewed by one other team member to assure accuracy.

Missing data

We will attempt to contact authors of included studies to obtain missing data considered important to summarize study findings.