Interim 1: October/2007

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

TITANIUM TETRACHLORIDE

(CAS Reg. No. 7550-45-0)

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Titanium tetrachloride is a colorless liquid that fumes when in contact with moist air. The odor of titanium tetrachloride has been described as penetrating, acrid, and irritating. The world-wide production of titanium tetrachloride was estimated at 6 million tons in 1996. Titanium tetrachloride is used in the manufacturing of titanium dioxide pigments, titanium metal, artificial pearls, and iridescent glass; in the production of Ziegler-Natto catalysts; and as a military smoke screen.

Titanium tetrachloride is highly corrosive. It hydrolyzes upon contact with moisture, releasing heat, hydrochloric acid, and orthotitanic acids, thereby causing direct tissue damage in the lung. Data indicate that the fine particulate oxychloride intermediates generated from titanium tetrachloride hydrolysis are able to penetrate deep into the lung where hydrolysis is completed, resulting in direct contact irritation and producing bronchitis or pneumonia. Skin (particularly moist skin) and eye contact with liquid titanium tetrachloride can result in severe, deep burns. Available data indicate that exposure to titanium tetrachloride fumes will also result in burns.

Human acute inhalation exposure data are confined to case studies in which the exposure concentrations were unknown. A fatal case reported in the secondary literature had severe pulmonary damage and destruction of the corneal tissue following accidental exposure to titanium tetrachloride fumes (Reisman, 1961). Non-fatal case reports had symptoms including a ticklish cough accompanied by an unpleasant taste in the mouth, cough and chest tightness and slight eye irritation (Ross, 1985); pulmonary findings similar to those found following thermal respiratory injury (Park et al., 1984); acute respiratory distress resulting from pneumonitis, findings of a moist lung with obstructive wheezing, and corneal damage (Reisman, 1961). A cross-sectional survey conducted to assess respiratory disease in titanium metal production workers reported an increase in pleural thickening and a non-related decrease in $FEV_{1.0}$ (Garabrant et al., 1987). It was hypothesized that these findings were the result of exposure to titanium tetrachloride and titanium dioxide particulate. No association was identified between titanium tetrachloride exposure and lung cancer (Fayerweather et al., 1992). No human developmental or reproductive inhalation toxicity data or human genotoxicity were available.

Acute toxicity data in dogs and rats demonstrate that death from titanium tetrachloride inhalation is the result of pulmonary edema (Kelly, 1980; Zapp, 1949). Humidity can affect the toxicity of titanium tetrachloride as was indicated by increased lethality in rats when humidity was increased (Burgess, 1977). LC_{50} values in rats ranged from 13,940 ppm for a 2-minute exposure to 59 ppm for a 4-hour exposure (Kelly, 1980). Clinical signs reported during exposure included eye closing and gasping, while signs noted after exposure consisted of corneal opacity, weight loss, and lung congestion. The severity of the signs was not provided for the various exposure concentrations and durations, but rather was given as a general statement. Histopathological examination revealed similar respiratory lesions in rats dying during exposure or post exposure, with death attributed to pulmonary edema. In the same study, Kelly (1980) assessed the reversibility of the respiratory tract lesions that developed in rats following a 30-minute exposure to the approximate LC_{10} (172 ppm). The severe respiratory tract irritation that was noted in rats at one day post exposure had resolved by 49 days post exposure. This study demonstrated that rats surviving an acute exposure to inhaled titanium tetrachloride should not

have any irreversible pulmonary effects. However, insufficient data were available to correlate irritant effects observed at nonlethal concentrations.

In a repeat-exposure study, groups of rats were exposed by inhalation for 6 hours/day, 5 days/week for 4 weeks to titanium tetrachloride hydrolysis products at measured concentrations of 0, 0.6, 1.3, or 5.2 ppm of titanium tetrachloride (Kelly, 1979). Exposure to 5.2 ppm resulted in the death of two rats during the study (one rat died on test day 15 and the other on test day 23); histopathological examination revealed that death was due to respiratory failure. No clinical signs were observed in rats exposed to 0.6 or 1.3 ppm, but rats exposed to 5.2 ppm exhibited labored breathing and slightly decreased body weight gain during the exposure interval that returned to normal following a recovery period. Clinical chemistry changes observed in the 1.3 and 5.2 ppm group were reversible (increased urine pH, decreased urine osmolality). Lung:body weight ratios were increased at terminal kill (126, 136, and 178% of controls for the 0.6, 1.3, and 5.2 ppm groups, respectively). The histopathological changes observed in the lungs of exposed rats at the 6- to 12-month recovery period (collagenized fibrosis) are likely the result of the repeated exposure scenario, as the Kelly (1979) study found that all pulmonary lesions following an acute inhalation exposure to the LC_{10} were resolved by 49 days post exposure.

The experimentally derived exposure values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, and k is a constant (ten Berge et al., 1986). To calculate n for titanium tetrachloride, a regression plot of LC_{50} values was derived using the 2, 5, 15, 30, 60, 120, and 240-minute LC_{50} values determined by Kelly (1980). From the regression analysis, the derived value of $n = 0.88$ was used in the temporal scaling of the AEGL values ($C^{0.88} \times t = k$).

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, derivation of an AEGL-1 is not recommended.

No acute toxicity data were relevant for derivation of an AEGL-2, so repeat-exposure studies were evaluated. One option for the AEGL-2 derivation would be to base the value on labored breathing reported in rats exposed to 5.2 ppm for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). There are several problems with this value, however. While it initially appeared that the deaths were due to repeated exposures to titanium tetrachloride, the deaths cannot be discounted. The Burgess (1977) study reported mortality in rats following a 4-hour exposure to 14 ppm. If one extrapolates this value over time to a 6-hour exposure, an exposure concentration of 8.8 ppm would be predicted to result in mortality. The strongest support that this level is too high is seen when one generates an AEGL-2 derivation based upon the 6-hour exposure to 5.2 ppm and extrapolates across time using the n value of 0.88: one obtains nearly identical values to those generated for the AEGL-3 derivation using a threshold for mortality as the endpoint.

Therefore, the AEGL-2 derivation is based upon the next lower exposure concentration of 1.3 ppm titanium tetrachloride for 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). No clinical signs were observed at this concentration. Based upon a lack of data identifying interspecies and intraspecies variability, a total uncertainty factor of 100 would normally be applied. However, the endpoint selected is below the endpoint defined for the AEGL-2 tier and the study was a multiple exposure study. Both of these factors make the starting value inherently

conservative. Therefore, a total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies). The experimentally derived exposure value is scaled to AEGL time frames using $C^{0.88} \times t = k$.

The mortality data by Kelly (1980) were used for the AEGL-3 derivation. This study was specifically designed to evaluate the mortality response for a wide range of exposure durations. One-third of the LC_{50} values are used for the AEGL-3 derivations. The adjusted empirical LC_{50} values for the 30, 60, and 240-minute exposure durations were used for the respective AEGL timepoints. Using an $n = 0.88$, the adjusted 15-minute LC_{50} value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC_{50} value was used to extrapolate to 480 minutes. An interspecies uncertainty factor of 3 was applied to the values because titanium tetrachloride is an irritant and the mechanism of action is therefore not expected to vary greatly among species. An intraspecies uncertainty factor of 3 was chosen because the mechanism of irritation is also not expected to vary greatly among subpopulations. Therefore, a total uncertainty factor of 10 was applied.

The calculated values are listed in the tables below.

Summary of Proposed AEGL Values for Name of Titanium Tetrachloride [ppm (mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	NR	NR	NR	NR	NR	NR: Not recommended due to insufficient data
AEGL–2 (Disabling)	7.6 (59)	2.2 (17)	1.0 (7.8)	0.21 (1.6)	0.094 (0.73)	Exposure of rats to 1.3 ppm for 6 h/d, 5 d/wk for 4 wks resulted in no clinical signs, but next exposure conc. approaches lethality threshold (Kelly, 1979)
AEGL–3 (Lethal)	38 (290)	13 (100)	5.7 (44)	2.0 (16)	0.91 (7.1)	One-third of rat LC_{50} values (Kelly, 1980)

1. INTRODUCTION

Titanium tetrachloride is a colorless liquid that fumes when in contact with moist air. The odor of titanium tetrachloride has been described as "penetrating, acrid" (Budavari et al., 1996) and irritating (AIHA, 1992). It is normally produced by the chlorination of titanium dioxide at high temperatures in the presence of a reducing agent (Kirk et al., 1997). The world-wide production of titanium tetrachloride was estimated at 6 million tons in 1996, and the main producers of titanium tetrachloride are the producers of titanium dioxide pigment. (Kirk et al., 1997). Titanium tetrachloride is used to manufacture titanium dioxide pigments, titanium metal, artificial pearls, and iridescent glass; in the production of Ziegler-Natto catalysts; and as a military smoke screen (Clayton and Clayton, 1994; Kirk et al., 1997). Titanium tetrachloride has a high affinity for water and is rapidly hydrolyzed. In water, a number of sequential reactions take place:

$$TiCl_4 + 5H_2O \rightarrow TiCl_3(OH) + 4H_2O + HCl \rightarrow TiCl_2(OH)_2 + 3H_2O + HCl \rightarrow$$
$$TiCl(OH)_3 + 2H_2O + HCl \rightarrow TiCl(OH)_4 + H_2O + HCl \quad \text{(Mezentseva et al., 1963).}$$

The production of the finely divided oxychlorides upon exposure to moist air is the basis for its use as white smoke by the military (Kirk et al., 1997):

$$TiCl_4 + H_2O \rightarrow TiOCl_2 + 2HCl$$

Skin (particularly moist skin) and eye contact with liquid titanium tetrachloride can result in severe, deep burns (Paulsen et al., 1998; Chitkara and McNeela, 1992; Lawson, 1961). Available data indicate that exposure to titanium tetrachloride fumes will also result in burns. Only a limited amount of data addressing the toxicity of inhaled titanium tetrachloride was available. Human data are confined to case studies in which the inhalation exposure concentrations were unknown. Animal studies in rats, mice, and dogs are available, but the studies are of limited usefulness because of poor reporting of experimental procedures and results, or because they were repeated exposure scenarios.

The physicochemical data of titanium tetrachloride are presented in Table 1.

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	tetrachlorotitanium; titanic chloride; titanium chloride	
Chemical formula	$TiCl_4$	
Molecular weight	189.71	
CAS Reg. No.	7550-45-0	
Physical state	colorless liquid colorless to light yellow clear liquid	Budavari et al., 1996 AIHA, 1992
Solubility in water	soluble in cold water, alcohol	Budavari et al., 1996
Vapor pressure	12 mmHg at 25EC	AIHA, 1992
Vapor density (air =1)	6.5	AIHA, 1996
Liquid density (water =1)	1.726 g/mL	Budavari et al., 1996
Melting point	-24.1EC	Budavari et al., 1996
Boiling point	136.4EC	Budavari et al., 1996
Conversion factors	1 ppm = 7.75 mg/m^3 1 mg/m^3 = 0.129 ppm	AIHA, 1992

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

The only case report of lethality following inhalation exposure to titanium tetrachloride was found in a secondary source (Reisman, 1961). A worker was admitted to the hospital in critical condition following inhalation of titanium tetrachloride fumes. Over the course of the four days preceding his death, the patient developed increasing respiratory and pulse rates, a high temperature, and mottled densities in the upper half of each lung as revealed by x-rays. He also had severe conjunctivitis with extensive destruction of the corneal tissue. He experienced increasing respiratory distress until death. Autopsy revealed pulmonary changes including congested upper lung lobes and brownish, rough bronchial mucosa with no purulent exudate. Microscopic examination of the lungs found marked hyperplasia with swollen cuboidal epithelium and marked cellular hyperplasia of the alveolar walls. A network of fibrin and the presence of a large amount of protein-like fluid containing polymorphonuclear leukocytes was seen in the alveolar spaces. The bronchial mucosa was hyperplastic and appeared somewhat like stratified epithelium. There were additional changes consistent with ulceration.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Three male workers confined in a 8.5 x 17 foot room with extraction ventilation were using titanium tetrachloride to assess a welding torch when a brass tap flew off and filled the room with titanium tetrachloride fumes (Ross, 1985). In addition to inhalation exposure, one worker also splashed titanium tetrachloride on his hand, which he proceeded to rinse off with water. The exposure was of a "short" duration (no further details provided). Following the exposure, one worker complained of a ticklish cough accompanied by an unpleasant taste in his mouth. A second worker developed a cough and tightness in his chest, and had slight eye irritation for approximately two hours post exposure. A third worker reported no symptoms. A medical examination (including a chest x-ray) of the workers "several hours later" did not reveal any abnormalities.

A 50-year-old chemical engineer was exposed when a glass pipe containing titanium tetrachloride broke, spraying his chest, head, neck, and back (Park et al., 1984). Although he was wearing a mask at the time of exposure, he removed it while running to the sink to wash off the chemical from his body. He was consequently exposed to the titanium tetrachloride fume for approximately 2 minutes. Twenty minutes following exposure, he developed a cough and dyspnea, and was taken to the hospital and admitted. Upon admission, the worker had second and third degree burns involving his chest, back, abdomen, arms, and scalp, and had erythema of the tongue, pharynx, and conjunctivae. Bilateral diffuse, expiratory wheezes were heard over his lungs. Shortly after admission, the patient was intubated and put on ventilation in response to signs of severe upper airway stridor. Progressive hypoxia and signs of respiratory distress syndrome were seen during the first 48 hours of hospitalization. He was taken off the ventilator at the end of the first week, but suffered several episodes of aspiration pneumonia requiring ventilation. A bronchoscopy conducted 11 days after admission revealed copious, thick yellow brown secretions in both lower lobes, areas of denuded mucosa, and eschar formation over the carina and several of the lobar spurs. A pulmonary embolus was discovered 3 weeks later, which responded to heparin treatment. Five weeks after admission, the patient developed respiratory insufficiency and CO_2 retention and required reintubation and ventilation. Bronchoscopy revealed erythema of the entire bronchial tree with thickening of the carina and all of the lobar and segmental spurs. Approximately 30-40 fleshy polypoid lesions were present on both sides of the bronchial trees. Biopsy revealed granulation tissue with acute inflammation. The polyps responded to treatment with high doses of corticosteroids. Bronchoscopy 4 and 6 weeks after corticosteroid administration revealed decreases in the number and size of polyps, but found stenosis and distortion of orifices. Pulmonary function tests revealed significant obstructive pulmonary involvement. The patient was discharged 12 weeks after admission, but returned one month later with tracheal stenosis requiring placement of a splint. Bronchoscopy one year after the accident revealed that many of the previously stenotic bronchial orifices returned to normal, with some degree of mild stenosis noted. The authors reported that similar pulmonary findings were observed in other cases following thermal respiratory injury.

In addition to the fatal case reported in secondary source (Reisman, 1961), seven nonfatal cases were also reported. One patient presented with acute respiratory distress, and x-rays revealed pneumonitis. Following antibiotic treatment, the patient had completely recovered

upon his release 14 days later. Six other cases presented with pulmonary findings of a moist lung with obstructive wheezing of an asthmatic type. No pulmonary changes were seen on x-ray, and the patients recovered within one to two days following treatment with oxygen, sedatives, and antibiotics. Of the seven additional case reports, four patients also had corneal damage.

2.2.2. Epidemiologic Studies

A cross-sectional survey was conducted to assess respiratory disease in titanium metal production workers (Garabrant et al., 1987). A group of 209 employees at a titanium metal production plant were evaluated by means of a health questionnaire (which evaluated the prevalence of chronic respiratory symptoms, past medical history, and smoking history), a physical examination, pulmonary function tests, and chest radiography. A complete occupational history including potential asbestos exposure was also obtained for each worker. Company records were obtained to classify each employee's work history. Three exposure groups were defined: reduction workers who worked at least six months in the reduction area (these workers were exposed to titanium tetrachloride vapor, titanium oxychloride, and titanium dioxide particles); chipping and washing workers who worked at least six months in the chipping and washing area but less than 6 months in the reduction area (these workers were exposed to a mixed aerosol of titanium, sodium chloride, and hydrochloric acid); and maintenance and service workers who worked less than six months in production jobs. No significant difference in the prevalence of symptoms was noted among groups. Pulmonary function tests revealed that reduction workers experienced a decrease in the $FEV_{1.0}$ (forced expiratory volume in 1 second) of 24 mL per year of employment in the reduction area after adjustment for age, height, and smoking. Unfortunately, no measurements of titanium tetrachloride were taken in the reduction area. An increase in pleural disease was associated with increasing duration of work in titanium manufacturing in general. However, no clear association was identified between pleural thickening and a reduced ventilatory capacity. The cause of the reduction in $FEV_{1.0}$ and of the pleural thickening observed in the titanium metal production workers was not clearly identified, but the author hypothesized they could be related to exposure to titanium tetrachloride and titanium dioxide particulates.

2.3. Developmental/Reproductive Toxicity

No human data addressing the potential for inhaled titanium tetrachloride to cause developmental or reproductive toxicity were found in the literature.

2.4. Genotoxicity

No human genotoxicity data were found in the available literature.

2.6. Carcinogenicity

Du Pont conducted a nested case-control study to assess the potential of occupational exposure to titanium tetrachloride to cause lung cancer (Fayerweather et al., 1992). The study cohort comprised male wage roll employees who worked for at least one year prior to 1984 at the

identified plant (workers started wearing respirators during routine operations with titanium tetrachloride starting in 1984). Cases were identified using the Du Pont mortality registry. The cases were defined "as all lung cancer deaths at the study plant who worked for at least one year at the plant prior to 1/1/84 and who died during the period 1935-1983." For each case that was selected, four controls were selected from the employee roster. These controls had to meet the following criteria: male gender, worked at the plant during the last year the case was employed at the plant, and match within 3 years the case's birth year and year of hire. Factors considered in the case control analyses included the duration of exposure, the cumulative exposure index (sum of products of duration and the range midpoint of each exposure level over all jobs held by the individual), and the time-weighted-average exposure (cumulative exposure index divided by the duration of exposure). In addition to birth year and year of hire, data were adjusted for smoking. No association was identified between titanium tetrachloride exposure and lung cancer (odds ratio 1.1; 90% C.I.: 0.4-3.2).

2.7. Summary

Human acute inhalation exposure data are confined to case studies in which the exposure concentrations were unknown. A fatal case reported in the secondary literature had severe pulmonary damage and destruction of the corneal tissue following accidental exposure to titanium tetrachloride fumes (Reisman, 1961). Non-fatal case reports had symptoms including: a ticklish cough accompanied by an unpleasant taste in his mouth, cough and chest tightness and slight eye irritation (Ross, 1985); pulmonary findings similar to those found following thermal respiratory injury (Park et al., 1984); and acute respiratory distress resulting from pneumonitis, findings of a moist lung with obstructive wheezing, and corneal damage (Reisman, 1961). A cross-sectional survey conducted to assess respiratory disease in workers exposed to titanium tetrachloride during titanium metal production reported an increase in pleural thickening and a non-related decrease in $FEV_{1.0}$ (Garabrant et al., 1987). It was hypothesized these findings were the result of exposure to titanium tetrachloride and titanium dioxide particulate. No association was identified between titanium tetrachloride exposure and lung cancer (Fayerweather et al., 1992). No human developmental or reproductive inhalation toxicity data or human genotoxicity were available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Dogs

To assess the effects of acute exposure, three dogs were exposed to titanium tetrachloride in a 10 m^3 chamber (Zapp, 1949). Titanium tetrachloride vapor was generated by placing liquid titanium tetrachloride in a dish under a fan. The chamber was filled with "roughly uniform concentrations of fumes" by turning on the fan intermittently. The actual exposure concentrations were not provided in the study details. Two dogs were exposed 4 times: on day one for 2 hours, day two for 1.5 hours, day eight for 1 hour, and day eleven for 2 hours. A third dog was exposed only once for 1 hour, and this dog's blood pressure, pulse and respiratory rate, and platelet count were followed for 3 days. All dogs exhibited respiratory distress during and after the exposures, and two dogs vomited during the exposure. One dog collapsed after the

second exposure, and was found dead in the exposure chamber following the fourth exposure. Necropsy of this dog revealed bronchitis and edema, and microscopic evaluation revealed small titanium particles in the bronchi and in a few alveoli. The other dog that was exposed four times was killed and necropsied four days after the last exposure. Gross necropsy of the lungs revealed focal congestion and hemorrhage with particulate matter deposits. Microscopic examination did not reveal any definitive pulmonary lesions, but the mucosa was thin and irregular, suggesting regeneration. The third dog that was exposed once for 1 hour exhibited a number of changes following exposure: blood pressure changed from 204/104 before exposure to 136/60 following exposure, pulse rate increased from 68 to 84, and respiration rate increased from 24 to 40. These parameters returned to normal the following day. Although the platelet count increased from 133,000 before exposure to 292,000 the second day post exposure, the values were still within the normal range for dogs. The dog was sacrificed and necropsied three days post exposure. A few minute hemorrhages were found toward the margins of the lung lobes, and small particles were found in the terminal bronchioles. No abnormalities were found in the trachea or bronchi.

3.1.2. Rats

Groups of six male ChR-CD rats (weighing between 240-300 g) were exposed by inhalation to various concentrations of titanium tetrachloride aerosol for 2, 5, 15, 30, 60, 120, or 240 minutes to determine the respective LC_{50} concentrations (Kelly, 1980). Animals were exposed head-only in a dynamic 33 L glass chamber. Titanium tetrachloride vapor was generated by bubbling dry cylinder air through liquid titanium tetrachloride (purity >99.5%), and the resultant vapor was diluted with 10 L/minute of air (60% relative humidity) in a mixing flask and passed into the exposure chamber. A yellow-white particulate cloud immediately formed as the titanium tetrachloride hydrolyzed. The exposure concentration was controlled by varying the water bath temperature and air flow rate through the bubbler. The exposure concentration was verified by trapping the particulate and vapor on a filter in tandem with an impinger containing a sodium acetate solution. The chamber titanium tetrachloride concentration was then calculated from the total chloride recovered from the filter and impinger solution using a chloride ion selective electrode. The chloride-measurement method was in agreement with atomic absorption measurements for titanium performed on several samples. Aerodynamic particle size ranged from 0.3 - 1.6 μm. Rats were exposed one at a time for the 2-minute exposures, while six rats at a time were exposed for the other exposure durations. Following exposure, the rats were observed for a 2-week period for mortality and were weighed daily. Major organs were examined and weighed at necropsy, and the respiratory tract was examined histopathologically.

Results of the acute lethality studies by Kelly (1980) are presented in Tables 2 and 3. Findings other than mortality were not reported for the individual exposure concentrations or durations, but were provided only as general findings. Clinical signs noted during exposure included eye closing and gasping, while signs noted after exposure consisted of corneal opacity, weight loss, and lung congestion. Histopathological examination revealed similar respiratory lesions in rats dying during exposure or post exposure, including inflamed airways, hypermucous secretion, epithelial denudation, severe necrotic laryngitis, pulmonary congestion, and hemorrhage. A white-gray powder was found in the airways, and necrotic keratitis and conjunctivitis were observed in the eyes. Death was the result of pulmonary edema.

To assess the reversibility of respiratory tract lesions, a group of rats surviving exposure to 172 ppm for 30 minutes (the approximate LC_{10}) was killed and examined two at a time after a recovery period of 1, 3, 7, 14, 21, or 49 days (Kelly, 1980). It was not stated how many rats were originally exposed. Severe respiratory inflammation was observed at one-day post exposure. The respiratory exudate was already organizing by three days post exposure, and by seven days post exposure, the acute inflammation had subsided, and the denuded epithelium was partially repaired. The respiratory lesions had almost completely disappeared and the epithelium was repaired by 14 and 21 days post exposure. Normal architecture had been restored by 49 days post exposure.

Table 2. Summary of LC_{50} Values for Rats Exposed to Titanium Tetrachloride

Time (min)	LC_{50} (ppm)	95% CL (ppm)	
		Lower	Upper
2	13,940	12690	17903
5	4600	3672	6945
15	713	479	1095
30	390	230	508
60	171	127	209
120	143	96	182
240	59	49	68

Data taken from Kelly, 1980.

Table 3. Summary of Lethality Data for Rats Exposed to Titanium Tetrachloride

Exposure duration (min)	Conc. (ppm)	Deaths [n=6]	Exposure duration (min)	Conc. (ppm)	Deaths [n=6]
2	9115	0	60	86	0
	11255	1		134	1
	11998	1		201	4
	12648	1		204	5
	11976	2		421	6
	16497	5	120	31	0
5	2163	0		105	1
	2736	0		178	4
	3117	3		222	6
	3055	1	240	35	0
	5277	3		52	1
	6890	5		66	5
15	296	1		83	6
	345	0			
	636	4			
	825	3			
	1039	4			
	1451	5			
30	108	0			
	293	2			
	379	5			
	458	3			
	510	3			
	538	3			
	569	4			
	692	6			

Data taken from Kelly, 1980.

Groups of six male ChR-CD rats (240-300 g) were exposed for four hours to concentrations of titanium tetrachloride ranging from 6 to 110 ppm with the relative humidity varying from 30%

to greater than 95% (at 25EC) (Burgess, 1977). Animals were exposed in a 125 L stainless steel and glass chamber with a total airflow of 35 L/min. The test atmosphere was generated by bubbling nitrogen through a gas bubbler containing titanium tetrachloride, followed by mixing with air. The titanium tetrachloride concentration was controlled by varying the nitrogen flow. Exposure concentrations were calculated using the total amount of chloride recovered. Chloride concentrations were determined by drawing chamber air through a midget impinger containing sodium hydroxide, passing it through a glass fiber filter, releasing the chloride ions using acetic acid, and measuring the number of ions using a chloride-ion specific electrode. Results of the lethality study are presented in Table 4. The only clinical sign noted was labored breathing that varied with exposure concentration. Mortality occurred either during or immediately after exposure. The investigator concluded that higher humidity resulted in increased toxicity as indicated by lethality, possibly the result of exposure to the increased production of the hydrolysis products from the reaction of titanium tetrachloride with the moisture in the air.

Table 4. Summary of Mortality of Rats Exposed to Titanium Tetrachloride for 4 Hours

Relative Humidity (%)	Chamber Conc.		Mortality (%) [n=6]
	mg/L	ppm	
30-35	0.044	6	0
	0.160	21	0
	0.160	21	0
	0.166	21	0
	0.296	38	6 (100)
	0.395	51	2 (33)
	0.473	61	5 (83)
	0.824	106	6 (100)
	0.855	110	5 (83)
60-65	0.045	6	0
	0.108	14	1 (17)
	0.111	14	1 (17)
	0.113	15	2 (33)
>95	0.170	22	2 (33)

Data taken from Burgess, 1977.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Four dogs were exposed to titanium tetrachloride vapor for 6 hours/day, 5 days/week for 45 exposures over a 70-day period (Zapp, 1949). The exposure concentrations of titanium

tetrachloride are not known, since chamber concentrations were reported only as the average concentration of titanium (8.4 ppm; range of 1.6 to 17.1 ppm) and chloride (6.8 ppm; range of 1.2 to 16.0 ppm). Dogs were observed for 6 weeks prior to exposure to establish a baseline. Blood pressure, body temperature, pulse rate, and respiratory rate were measured 2/day for 5 days/week, and blood and urine samples were collected and analyzed biweekly. These measurements were continued throughout the exposure. During exposure, no consistent effects on blood pressure were observed. No significant changes in red blood cell or hemoglobin concentrations were noted, but the leukocyte count increased in three of the dogs during the experiment (not statistically significant). No changes in body weight, blood, or urine chemistry were observed. Dogs were killed and necropsied three days after the last exposure. Pathological changes were observed only in the lungs. Gross necropsy revealed numerous dull red spots in the lungs, and microscopic examination revealed numerous monocytes (dust cells, macrophages, and phagocytes) distended with brown granules scattered diffusely throughout the lung, with a grouping noted around the bronchi. The brown granules were identified as titanium. Evidence of a reparative process was indicated by connective tissue proliferation in the vicinity of the monocytes. The centers of the largest lesions contained necrotic material most likely derived from monocytes, alveolar cells, and perhaps other unidentified cells. The author compared the microscopic pulmonary damage to that produced by silica exposure.

3.2.2. Rats

In a study designed to assess sensory irritation, groups of four male, ChR-CD rats were exposed head-only for 20 minutes to titanium tetrachloride concentrations ranging from 5 to 555 ppm (Gardner, 1980). Titanium tetrachloride vapor was generated by passing a stream of nitrogen over liquid titanium tetrachloride, and diluting with humidified air before passing into the chamber. The hydrolysis products formed a dense, white aerosol. Exposure concentrations were verified by analyzing two air samples taken during each exposure. The chamber air samples were drawn through midget impingers connected in series containing sodium acetate as the trapping solvent, and then analyzed using a chloride specific ion electrode. Following exposure, animals exhibited lacrimation and clear nasal discharge. Exposed animals also exhibited a “mild” weight loss (actual values not provided) within 24 hours post exposure, with normal weight gain thereafter. The percentage of the respiratory rate change is presented in Table 5. Exposure to 5 or 14 ppm titanium tetrachloride resulted in increased respiration, with higher exposure concentrations resulting in decreased respiration. The calculated RD_{50} was 313 ppm.

Table 5. Percentage of Respiratory Rate Change in Rats Exposed to Titanium Tetrachloride

Conc. (ppm)	% Respiratory Rate Change
5	+18.2
14	+6.0
26	-12.0
41	-17.8
159	-42.5
361	-63.3
379	-62.0
555	-75.5

Taken from Gardner, 1980

Groups of 25 ChR-CD male rats were exposed by inhalation for 6 hours/day, 5 days/week, for 4 weeks to titanium tetrachloride hydrolysis products at measured concentrations of 0, 0.6, 1.3, or 5.2 ppm (reported as 0, 1, 10, or 40 mg/m^3) titanium tetrachloride (Kelly, 1979). Exposures were conducted in a 1.3 m^3 dynamic stainless steel inhalation chamber, and test material atmosphere was generated by passing a stream of nitrogen over liquid titanium tetrachloride followed by mixing with the chamber air supply. Chamber concentrations were analytically verified by measuring the total amount of chloride recovered. Chamber air was drawn through a midget impinger containing sodium hydroxide, and then passed through a glass filter to collect particulates. The glass filter was dropped into the impinger solution followed by a pH adjustment, and the total chloride content was measured using a chloride ion-specific electrode and comparing to a standard. Animals were observed daily and weighed weekly. Clinical testing (hematology, clinical chemistry, and urinalysis) was performed on 10 rats/group on the last exposure day and after a 2-week recovery period. Blood and urine δ-aminolevulinic (ALA) assays were conducted at one week intervals during exposure and after a 2-week recovery period. Five rats/group were killed and examined grossly and microscopically on the last exposure day, and after 2 weeks, 3 months, 6 months, or 12 months post exposure.

Two rats from the 5.2 ppm group died on test day 15 and 23 from respiratory failure (Kelly, 1979). Pathological examination of these animals revealed partial dust obstruction of the trachea, denuded tracheal epithelium, acute obliterative bronchiolitis, interstitial pneumonitis and pulmonary edema and hemorrhage. Clinical signs noted in the 5.2 ppm group included labored breathing and slightly decreased body weight gain over the exposure interval (approximately 93% of controls), but these rats returned to normal during the recovery period. No clinical signs were observed in rats exposed to 0.6 or 1.3 ppm. Clinical chemistry analysis revealed changes in the 1.3 and 5.2 ppm groups including statistically decreased urine osmolality (87 and 80% of controls, respectively) and increased urine pH (7.68 and 7.8, respectively, vs. 7.2 for the controls). Additional changes in the 5.2 ppm group included decreased BUN (74% of controls) levels and decreased blood ALA levels throughout exposure. All of these clinical chemistry

changes returned to normal values following a 2-week recovery period and were not accompanied by any corresponding pathological changes. Gross necropsy revealed increased lung:body weight ratios in all groups of rats killed on the last day of exposure (+26%, +36, and +78% of controls for the 0.6, 1.3, and 5.2 ppm groups, respectively), with 2-weeks post exposure values still increased in the 1.3 and 5.2 ppm groups (+14% and +28%, respectively). Lung:body weight ratios returned to values comparable to controls by 3 months post exposure. Pathological examination of exposed rats revealed a mild dust-cell reaction in 0.6 ppm rats observed up to one year post exposure. At the end of the exposure period, the 1.3 and 5.2 ppm group rats exhibited a concentration-dependent acute inflammation of the respiratory tract. Following a 2-week recovery period, inflammation had subsided in these groups and repair was indicated by proliferated alveolar fibroblasts and thickened alveolar walls. By 3-months post-exposure, dust-cell foci were seen in the respiratory bronchioles and adjacent alveoli, with some areas of patchy fibrosis with collagen deposition. At 6 to 12 months post exposure, a decrease was observed in the dust cell foci and thickened alveolar walls. Collagenized fibrosis was evident, particularly in the respiratory bronchioles and adjoining alveolar walls.

3.3. Developmental/Reproductive Toxicity

No data were found that addressed the potential for inhaled titanium tetrachloride to cause developmental or reproductive toxicity in animals.

3.4. Genotoxicity

Titanium tetrachloride at concentrations of 1-10,000 µmoles/plate was not mutagenic to *Salmonella typhimurium* strains TA1537, TA2637, TA98, TA100, or TA102 (Ogawa et al., 1987). Titanium tetrachloride also tested negative in a modified *Salmonella typhimurium* test system, in which 100 µmoles of 9-aminoacridine was added to the test plates (Ogawa et al., 1987). Titanium tetrachloride was toxic in this test system at a concentration of 5000 µmoles/plate. Titanium tetrachloride was not mutagenic in the CHO/HGPRT assay (test concentrations not provided) (Hsie et al., 1979).

3.5. Chronic Toxicity/Carcinogenicity

Groups of 100 male and 100 female Crl:CD rats were exposed to 0, 0.013, 0.13, or 1.3 ppm (reported as 0, 0.1, 1.0, or 10 mg/m^3) of titanium tetrachloride aerosol for 6 hours/day, 5 days/week for 24 months (Lee et al., 1986). Five male and five female rats from each group were killed at 3 and 6 months of exposure and ten male and ten female rats were killed at one year of exposure for gross and microscopic evaluation. Animals were exposed to titanium tetrachloride vapor in a chamber made of high-nickel, stainless-steel designed to withstand the corrosive nature of the vapor. The vapor was generated by passing nitrogen over liquid titanium tetrachloride in a glass vessel maintained at 20EC, followed by mixing with a 1000 L/min chamber air supply. The chamber concentrations were measured by trapping the solid titanium tetrachloride hydrolysis products on cellulose acetate filters, followed by analysis with a colorimetric method. The exposure concentrations were reported as mg/m^3 of titanium tetrachloride as calculated from the titanium concentration. Aerodynamic analysis of chamber

particulates revealed that almost all particles were less than 1.6 FM. Analysis of chamber air revealed almost no unhydrolyzed titanium tetrachloride in the chamber.

No exposure-related differences were observed in clinical signs, body weight changes, morbidity, or mortality in rats exposed for 2 years (Lee et al., 1986). Increased lung weights were observed in high-concentration males and females (+32 and +54% of controls respectively). Histopathological examination revealed only mild rhinitis in rats exposed to 0.013 ppm. Rats exposed to 0.13 ppm had increased incidences of rhinitis and tracheitis, and slight hyperplasia of Type II pneumocytes enclosing dust cells in the alveoli. The pulmonary changes observed at 0.13 ppm were consistent with those caused by a nuisance dust. Pulmonary findings in rats exposed to 1.3 ppm were more substantial, and included hyperplasia of Type II pneumocytes enclosing dust cells in the alveoli, alveolar bronchiolarization, cholesterol granulomas (with associated foamy macrophages), alveolar proteinosis, and focal pleurisy. Particle deposition observed in the tracheobronchial lymph nodes in rats exposed to 0.13 or 1.3 ppm and in the liver and spleen of rats exposed to 1.3 ppm was not considered biologically significant because there was no evidence of tissue damage or of a cellular response. The finding of squamous cell carcinomas in the area of the alveoli in 2/69 males and 3/74 females in the 1.3 ppm exposure group compared with no findings in any of the other exposed or control rats is of uncertain relevance to humans. Two cases were keratinized cystic squamous cell carcinomas (with no invasion into adjacent tissue), and the other three were microscopic-sized, well-differentiated squamous cell carcinomas. The authors classified the lesions as cystic keratinizing squamous cell carcinoma, indicating that there are no accepted classifications of these benign lung lesions.

3.6. Summary

The only acute inhalation exposure studies in animals with quantified exposure concentrations of titanium tetrachloride were in rats. One study investigating the effect of varying humidity on titanium tetrachloride toxicity reported higher humidity resulted in increased toxicity as indicated by lethality (Burgess, 1977). Another study reported LC_{50} values ranging from 13,940 ppm for a 2-minute exposure to 59 ppm for a 4-hour exposure (Kelly, 1980). Clinical signs noted in rats during exposure included eye closing and gasping, while signs noted after exposure consisted of corneal opacity, weight loss, and lung congestion. The severity of the signs was not provided for the various exposure concentrations and durations, but rather was given only as a general statement. Histopathological examination revealed similar respiratory lesions in rats dying during exposure or post exposure, with death attributed to pulmonary edema. Necrotic keratitis and conjunctivitis was observed in the eyes. A further study investigating the reversibility of the respiratory tract lesions demonstrated that rats surviving an acute exposure to inhaled titanium tetrachloride should not have any irreversible pulmonary effects. However, insufficient data were available to correlate irritant effects observed at the nonlethal concentrations reported in Kelly (1980).

An RD_{50} value of 313 ppm in CHR-CD rats was reported (Gardner, 1980). Substantial differences have been observed between species in their response to irritants, and for this reason the standard RD_{50} testing protocol calls for the use of male Swiss-Webster mice only (Alarie et

al., 1980; ASTM, 1991). Therefore, the RD_{50} value generated in this study is questionable for use in AEGL derivations.

A four-week exposure study in rats reported two deaths in the high-concentration group exposed to 5.2 ppm (Kelly, 1979). The deaths were the result of severe pulmonary effects. No clinical signs were observed in rats exposed to 0.6 or 1.3 ppm, but rats exposed to 5.2 ppm exhibited labored breathing and a slightly decreased body weight gain over the exposure interval that returned to normal following a recovery period. Clinical chemistry changes observed in the 1.3 and 5.2 ppm groups were reversible. The histopathological changes observed in the lungs of exposed rats at the 6- to 12-month recovery period (collagenized fibrosis) are likely the result of the repeated exposure scenario, as the Kelly (1979) study found that all pulmonary lesions following an acute inhalation exposure to the LC_{10} were resolved by 49 days post exposure.

Dogs exposed to high (but unknown) concentrations of titanium tetrachloride for 4 exposures of 1.5-2 hours over eleven days exhibited respiratory distress during and after the exposures, with one dog dying after the fourth exposure from pulmonary toxicity (bronchitis and edema), and the second dog developing focal congestion and hemorrhage by sacrifice four days post exposure (Zapp, 1949). A third dog exposed once for 1 hour developed histopathological changes of a few minute pulmonary hemorrhages by sacrifice at three days post exposure. Repeated titanium tetrachloride inhalation exposure over 10 weeks revealed pulmonary effects in dogs consistent with damage produced by silica exposure (Zapp, 1949).

A 2-year chronic toxicity and carcinogenicity bioassay in rats reported effects of mild irritation (rhinitis) at 0.013 ppm, a pulmonary response consistent with a nuisance dust at 0.13 ppm, and pulmonary lesions in the alveolar duct region where dust cells accumulated, evoking a chronic tissue response at 1.3 ppm of titanium tetrachloride (Lee et al., 1986). Squamous cell carcinomas in the area of the alveoli in 2/69 males and 3/74 females in the 1.3 ppm exposure group compared with no findings in any of the other exposed or control rats were of uncertain relevance to humans.

No developmental or reproductive inhalation toxicity data were available. Titanium tetrachloride was not mutagenic in the *Salmonella typhimurium* test system (Ogawa et al., 1987) or in the CHO/HGPRT assay (Hsie et al., 1979).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

A group of 12 white rats were exposed for one hour to an approximate concentration of 260 ppm of titanium tetrachloride (Sanotskij and Babina, 1962). Animals were killed by decapitation immediately after, 24 hours after, or 6 days after exposure, and the concentration of titanium was determined in the blood, lungs, intestines (with contents), liver, and brain. The concentration in the urine was also determined following collection in metabolism cages. One animal died during the exposure. Following the exposure, approximately 28 µg/g titanium was found in the lungs and 10 µg/g was recovered in the blood. The concentration in the blood dropped to less than 1 µg/g by one day post exposure, while the concentration in the lungs dropped to 22 µg/g by one

day and 15 µg/g by six days post exposure. The intestines were the main route of elimination with 25 µg/g recovered at one day post exposure and 4 µg/g six days post exposure. The concentration of titanium in the urine was 11 µg/g one day post exposure, 7 µg/g three days post exposure, and less than 1 µg/g six days post exposure. Liver and brain had low concentrations of titanium: approximately 1 µg/g by day 6 post exposure.

4.2. Mechanism of Toxicity

Titanium tetrachloride is highly corrosive, hydrolyzing upon contact with moisture releasing heat, hydrochloric acid, and orthotitanic acids. The pulmonary damage induced by inhaled titanium tetrachloride does not appear to be due to the generation of only hydrogen chloride. Kelly (1980) reported that titanium tetrachloride exposure in rats resulted in greater lethality than what would be expected based on its hydrogen chloride (HCl) formation. On a molar basis, titanium tetrachloride was 16 times more toxic than what would be predicted. Kelly proposed that the fine particulate oxychloride intermediates generated from titanium tetrachloride hydrolysis penetrate deeper into the lung where hydrolysis is completed, whereas hydrogen chloride is primarily absorbed along the upper respiratory tract.

In a study designed to assess the toxicity of the hydrolysis products of titanium tetrachloride compared to HCl, groups of five white mice were exposed to various concentrations of titanium tetrachloride or HCl in a 100 L chamber for two hours (Mezentseva et al., 1963). HCl was generated from the reaction between concentrated sulfuric acid and table salt, while titanium tetrachloride was placed in a petri dish in the chamber where it evaporated and was simultaneously hydrolyzed. The exposure concentrations of titanium tetrachloride were based upon the concentration of HCl generated. Animals were observed during the 2-hour exposure, and then observed for mortality up to ten days post exposure. Further protocol details (such as measurement of exposure concentrations, sex of the animals, and use of control animals) were not provided. Study results are presented in Table 6. The hydrolysis products of titanium tetrachloride resulted in more mortality than HCl alone, but pure HCl resulted in a stronger local effect as demonstrated by the behavior of the animals and damage to the mucous membranes of the upper respiratory tract and necrosis of the conjunctiva. The authors then investigated the degree of development of edema following exposure to pure HCl or titanium tetrachloride hydrolysis products as measured by the pulmonary coefficient K = [weight of lungs (g)/ body weight (g)]. They found that pulmonary edema developed following exposure to HCl derived from the hydrolysis of titanium tetrachloride, but not with similar concentrations of pure gaseous HCl. The authors hypothesized this was due to the action of titanium oxide hydrates, which would absorb the HCl produced and carry it deeper into the lungs. Therefore, the titanium tetrachloride-generated HCl could reach the alveoli where it could undergo further hydrolysis. Pure HCl, on the other hand, is so soluble that it reacts primarily in the nasopharynx and trachea.

In conclusion, titanium tetrachloride is highly corrosive, hydrolyzing upon contact with moisture releasing heat, hydrochloric acid, and orthotitanic acids, thereby causing direct tissue damage in the lung. Data indicate that the fine particulate oxychloride intermediates generated from titanium tetrachloride hydrolysis are able to penetrate deep into the lung where hydrolysis is completed, resulting in direct contact irritation and producing bronchitis or pneumonia.

Table 6. Comparative Toxicity of Titanium Tetrachloride Hydrolysis Products and of HCl

Concentration (mg/L)		Number exposed	Time of first death (min)	Mortality		
Ti	HCl			During exposure	After exposure	Total
Products of titanium tetrachloride hydrolysis						
0.3-0.03	0.24	5	3	4	-	4 (80%)
0.24-0.02	0.018-0.01	5	3	2	1	3 (60%)
0.15-0.01	0.07-0.005	5	35	1	1	2 (40%)
HCl						
-	0.24-0.03	5	-	-	1	1 (20%)
-	0.11-0.036	5	-	-	-	0
-	0.06-0.012	5	-	-	-	0

Taken from Mezentseva et al., 1963, p. 41.

4.3. Structure Activity Relationships

Structure-activity relationships were not used in the derivation of AEGLs. As discussed in the Mechanism section (4.2.), exposure of titanium tetrachloride results in greater toxicity than what would be expected based on molar equivalents of HCl produced.

4.4. Other Relevant Information

4.4.1. Species Variability

Titanium tetrachloride is an irritant and the mechanism of toxicity is a direct contact effect; therefore, the mechanism of action is not expected to vary greatly among species. It is recognized that rodents are obligate nose breathers, and it is likely that titanium tetrachloride will react higher in the respiratory tract (especially the nasal cavity) compared to humans.

4.4.2. Susceptible Populations

Individuals with asthma may respond to exposure to respiratory irritants such as titanium tetrachloride with increased bronchial responsiveness. However, no information on the relative susceptibility of asthmatic and normal individuals to titanium tetrachloride was located.

4.4.3. Concentration-Exposure Duration Relationship

The experimentally derived exposure values are scaled to AEGL time frames using the concentration-time relationship given by the equation $C^n \times t = k$, where C = concentration, t = time, and k is a constant. The values of the exponent n generally are in the range of 1-3.5, and

"should always be derived empirically from acute inhalation toxicity experiments, in which both the concentration and exposure period are variables" (ten Berge et al., 1986). To calculate *n* for titanium tetrachloride, a regression plot of LC_{50} values was derived using the 2, 5, 15, 30, 60, 120, and 240-minute LC_{50} values determined by Kelly (1980) (see Table 2 for LC_{50} values; Appendix B for calculation of *n*). From the regression analysis, the derived value of $n = 0.88$ was used in the temporal scaling of the AEGL values ($C^{0.88} \times t = k$).

4.4.4. Concurrent Exposure Issues

In an occupational setting, workers exposed to titanium tetrachloride would likely also be exposed to hydrogen chloride and titanium dioxide. Inhaled titanium dioxide is relatively innocuous, with the primary concern being that of a nuisance dust. As already discussed, hydrogen chloride is one of the hydrolysis products of titanium tetrachloride.

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Human data were not relevant to the derivation of AEGL-1. Although the odor of titanium tetrachloride has been described as penetrating and acrid, no odor threshold data are available.

5.2. Summary of Animal Data Relevant to AEGL-1

No acute animal toxicity data were relevant to the derivation of an AEGL-1. Insufficient data were available to correlate irritant effects observed at nonlethal concentrations reported in Kelly (1980). A repeat-exposure study reported that rats exposed to 0.6 or 1.3 ppm for 6 hours/day, 5 days/week for 4 weeks exhibited no clinical signs, and the clinical chemistry changes observed in the 1.3 group were reversible (Kelly, 1979). The histopathological changes observed in the lungs of exposed rats at the 6- to 12-month recovery period are the result of the repeat-exposure scenario, as the Kelly (1979) study found that all pulmonary lesions following an acute inhalation exposure to the LC_{10} were resolved by 49 days post exposure.

5.3. Derivation of AEGL-1

No data relevant to the definition of an AEGL-1 endpoint are available. Therefore, derivation of AEGL-1 values is not recommended.

TABLE 7. AEGL-1 Values for Titanium Tetrachloride [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
NR	NR	NR	NR	NR

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data were relevant to the derivation of AEGL-2 values. Case reports of accidental workplace exposures did not contain information about exposure concentration and duration.

6.2. Summary of Animal Data Relevant to AEGL-2

Acute animal toxicity data are not appropriate for deriving an AEGL-2. Insufficient data were available to correlate irritant effects observed at nonlethal concentrations reported in Kelly (1980).

In a repeat-exposure study, groups of rats were exposed by inhalation for 6 hours/day, 5 days/week for 4 weeks to titanium tetrachloride hydrolysis products at measured concentrations of 0, 0.6, 1.3, or 5.2 ppm of titanium tetrachloride (Kelly, 1979). Exposure to 5.2 ppm resulted in the death of two rats during the study (one rat died on test day 15 and the other on test day 23), histopathological examination revealed that death was due to respiratory failure. No clinical signs were observed in rats exposed to 0.6 or 1.3 ppm, but rats exposed to 5.2 ppm exhibited labored breathing and a slightly decreased body weight gain during the exposure interval that returned to normal following a recovery period. Clinical chemistry changes observed in the 1.3 and 5.2 ppm group were reversible (increased urine pH, decreased urine osmolality). Lung:body weight ratios were increased at terminal kill (126, 136, and 178% of controls for the 0.6, 1.3, and 5.2 ppm groups, respectively). The histopathological changes observed in the lungs of exposed rats at the 6- to 12-month recovery period (collagenized fibrosis) are likely the result of the repeated exposure scenario, as the Kelly (1979) study found that all pulmonary lesions following an acute inhalation exposure to the LC_{10} were resolved by 49 days post exposure.

6.3. Derivation of AEGL-2

Because of the irritating properties of this chemical, the AEGL-2 should be based on irritation. One option for the AEGL-2 derivation would be to base the value upon the labored breathing reported in rats exposed to 5.2 ppm for 6 hours/day, 5 days/week for 4 weeks, but there are several problems with this value (Kelly, 1979). Although it initially appears that the deaths were due to repeated exposures to titanium tetrachloride, the deaths cannot be discounted. The Burgess (1977) study reported mortality in rats following a 4-hour exposure to 14 ppm. If one extrapolates this value over time to a 6-hour exposure, an exposure concentration of 8.8 ppm would be predicted to result in mortality. However, the strongest support that this level is too high is seen when one actually generates an AEGL-2 derivation based upon the 6-hour exposure to 5.2 ppm and extrapolates across time using the n value of 0.88: one obtains nearly identical values as those generated for the AEGL-3 derivation using a threshold for mortality as the endpoint.

Therefore, the AEGL-2 derivation is based upon the repeat-exposure study in which rats were exposed to 1.3 ppm titanium tetrachloride 6 hours/day, 5 days/week for 4 weeks (Kelly, 1979). No clinical signs were observed at this concentration. Based upon a lack of data identifying interspecies and intraspecies variability, a total uncertainty factor of 100 would

normally be applied. However, the endpoint selected is below the endpoint defined for the AEGL-2 tier in addition to the fact that the study was a multiple exposure study. Both of these factors make the starting value inherently conservative. Therefore, a total uncertainty factor of 10 was applied (3 for interspecies and 3 for intraspecies). The value was then scaled across time using the derived value of n=0.88 (see Section 4.4.3.; Appendix B). The proposed AEGL-2 values are presented in Table 8.

TABLE 8. AEGL-2 Values for Titanium Tetrachloride [ppm (mg/m^3)]

10-minute	30-minute	1-hour	4-hour	8-hour
7.6 (59)	2.2 (17)	1.0 (7.8)	0.21 (1.6)	0.094 (0.73)

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data were relevant to the derivation of AEGL-3.

7.2. Summary of Animal Data Relevant to AEGL-3

An extensive mortality study determined the LC_{50} values for exposure durations ranging from 2 minutes up to 4 hours (Kelly, 1980). A range-finding study investigated the effects of differing relative humidity on the approximate lethal concentration of a 4-hour exposure (Burgess, 1977).

7.3. Derivation of AEGL-3

The mortality data by Kelly (1980) were used for the AEGL-3 derivation. This study was specifically designed to evaluate the mortality response for a wide range of exposure durations. Using the raw mortality data, the LC_{01} was calculated for the various exposure concentrations, and the results are presented in Table 9. When sufficient information is available, the preferred method for AEGL-3 derivation utilizes probit analysis to determine the LC_{01}. When viewing the LC_{01} data, however, one sees the animal response at 1-hour was such that the 1-hour LC_{01} is greater than the 30-minute LC_{01}. This is because the response of the animals started to vary at this time point (as evidenced by the slope; see Table 11). When the LC_{01} values are not available, another method of estimating the lethality threshold is dividing the LC_{50} value by 3 (values presented in Table 9). One can see that although these values (one-third the LC_{50} values) for the shorter exposure durations are greater than the LC_{01} values, they are generally less than or comparable to the highest concentration causing no mortality. Therefore, one-third of the LC_{50} values are used for the AEGL-3 derivations.

Table 9. Summary of Lethality Data Used for AEGL-3 Derivation					
Time (min)	LC_{50} [a] (ppm)	⅓ of LC_{50} (ppm)	LC_{01} [a]		Highest Conc. with No Mortality
			Value (ppm)	slope	
2	13,940	4600	9043	12	9115
5	4600	1500	1591	5	2736
15	713	240	138	3	345[b]
30	390	130	89	4	108
60	171	57	96	9	86
120	143	48	74	8	31
240	59	20	44	19	35

[a] Values calculated by Kelly, 1980

[b] Although this concentration resulted in no mortalities, the lower concentration of 296 ppm resulted in one mortality. Therefore, this value may not be representative of the threshold for lethality.

The adjusted empirical LC_{50} values for the 30, 60, and 240-minute exposure durations were used for the respective AEGL timepoints. Using an $n = 0.88$, the adjusted 15-minute LC_{50} value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC_{50} value was used to extrapolate to 480 minutes. An interspecies uncertainty factor of 3 was applied to the values because titanium tetrachloride is an irritant and the mechanism of action is therefore not expected to vary greatly among species. An intraspecies uncertainty factor of 3 was chosen because the mechanism of irritation is also not expected to vary greatly among subpopulations. Therefore, a total uncertainty factor of 10 was applied. The proposed AEGL-3 values are presented in Table 10.

TABLE 10. AEGL-3 Values for Titanium Tetrachloride [ppm (mg/m^3)]				
10-minute	30-minute	1-hour	4-hour	8-hour
38 (290)	13 (100)	5.7 (44)	2.0 (16)	0.91 (7.1)

8. SUMMARY OF PROPOSED AEGLS

8.1. AEGL Values and Toxicity Endpoints

A summary of the AEGL values is presented in Table 11. An AEGL-1is not recommended due to insufficient data. The AEGL-2 is based upon a 1.3 ppm exposure in rats for 6 hours/day, 5 days/week for 4 weeks. Although no clinical signs were reported at this concentration, exposure to the next higher concentration (resulting in labored breathing) approached the lethality threshold concentration. The AEGL-3 values are based upon one-third of LC_{50} values in rats (Kelly, 1980).

TABLE 11. Summary of AEGL Values [ppm(mg/m^3)]

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2 (Disabling)	7.6 (59)	2.2 (17)	1.0 (7.8)	0.21 (1.6)	0.094 (0.73)
AEGL-3 (Lethal)	38 (290)	13 (100)	5.7 (44)	2.0 (16)	0.91 (7.1)

A useful way to evaluate the AEGL values in context of existing empirical data is presented in Figure 1. For this plot, the toxic response was placed into severity categories. The severity categories fit into definitions of the AEGL health effects: 0 = no effects; 1 = discomfort; 2 = disabling; 3 = lethal, and SL = partially lethal (an experimental concentration at which some of the animals died and some did not). The effects that place an experimental result into a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The concentrations often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is placed on a log scale. The graph in Figure 1 plots the titanium tetrachloride AEGL values along with the existing acute animal toxicity data for titanium tetrachloride in terms of the categories assigned to them. From this plot, one sees that the AEGL values are below any exposure concentration in animals resulting in any effects, and should therefore be protective of human health.

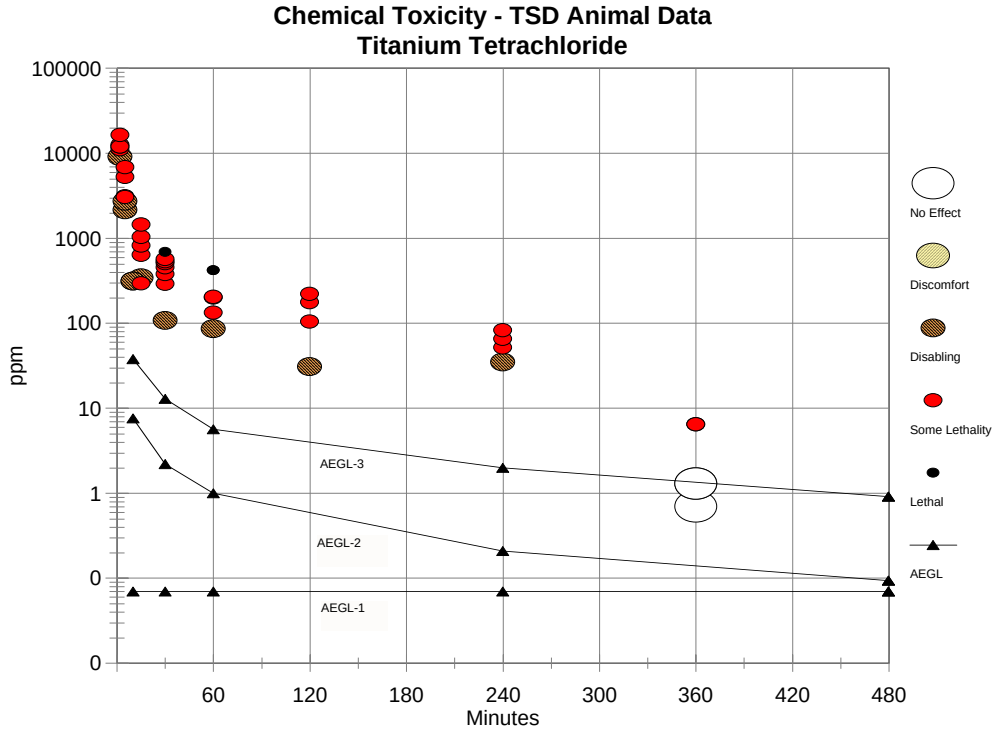

Figure 1. Category Plot of Animal Toxicity Data Compared to AEGL Values

8.2. Comparison with Other Standards and Guidelines

Occupational standards developed for titanium tetrachloride are limited to the AIHA WEEL and ERPG (see Table 12). The only titanium compound for which an OHSA occupational standard has been derived is for titanium dioxide, which has a PEL of 15 mg/m^3, the standard given for total dust.

TABLE 12. Extant Standards and Guidelines for Titanium Tetrachloride [ppm (mg/m^3)]

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2	7.6 (59)	2.2 (17)	1.0 (7.8)	0.21 (1.6)	0.094 (0.73)
AEGL-3	38 (290)	13 (100)	5.7 (44)	2.0 (16)	0.91 (7.1)
ERPG-1 (AIHA)[a]			0.65 (5)		
ERPG-2 (AIHA)			2.6 (20)		
ERPG-3 (AIHA)			13 (100)		
WEEL (AIHA)[b]					0.06 (0.5)

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 1992; 2004)

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for titanium tetrachloride is 5 mg/m3: this concentration could theoretically release up to approximately 3 ppm of hydrogen chloride (which has an ERPG-1 of 3 ppm). This concentration should produce health effects no more serious than mild irritation to the skin and eyes.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for titanium tetrachloride is 20 mg/m^3: this concentration could theoretically release up to approximately 10 ppm of hydrogen chloride (which has an ERPG-2 of 10 ppm). Higher concentrations may cause serious irritation to eyes, respiratory tract, and might impair escape. Concentrations of 15-20 mg/m^3 were tolerated well by workers exposed for a short time.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for titanium tetrachloride is 100 mg/m^3: this concentration could theoretically release up to approximately 50 ppm hydrogen chloride (which has an ERPG-3 of 100 ppm).

[b]**WEEL (Workplace Environmental Exposure Levels, American Industrial Hygiene Association** (AIHA 1996; 2004). AIHA WEELs represent the workplace exposure levels to which it is believed nearly all employees could be exposed repeatedly without adverse health effects. The WEEL for titanium tetrachloride is based on a NOAEL of 1.0 mg/m^3 and minimal effects at 10 mg/m^3 in rats exposed 6 hr/day, 5 days/week for 2 years.

As discussed, one of the hydrolysis products of titanium tetrachloride is hydrogen chloride. Therefore, the AEGL values for hydrogen chloride are presented in Table 13 for comparison. The Kelly (1980) study reported a 16-fold difference in potency of titanium tetrachloride compared to that expected from HCl exposure alone. The redlined values in Table 13 are the HCL AEGL values divided by 16 for ease of comparison to the proposed titanium tetrachloride AEGL values.

Table 13. AEGL Values for Hydrogen Chloride [ppm (mg/m^3)]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.8 (2.7) 0.11*	1.8 (2.7) 0.11*	1.8 (2.7) 0.11*	1.8 (2.7) 0.11*	1.8 (2.7) 0.11*	No-adverse-effect-level in exercising human asthmatics
AEGL-2 (Disabling)	100 (156) 6.3*	43 (65) 2.7*	22 (33) 1.4*	11 (17) 0.69*	11 (17) 0.69*	Mouse RD_{50} ; Histopathology in rats
AEGL-3 (Lethal)	620 (937) 39*	210 (313) 13*	100 (155) 6.3*	26 (39) 1.6*	26 (39) 1.6*	Estimated NOEL for death from 1-hour rat LC_{50}

* These values are the HCL AEGL values in ppm divided by 16, the estimated difference in potency between titanium tetrachloride and HCl.
Taken from: NRC (2004).

8.3. Data Adequacy and Research Needs

Data available for titanium tetrachloride AEGL derivations are limited. The only acute human data are case reports of exposure with unknown concentrations or durations. A cross-sectional survey was available, but this study had unquantified exposure concentrations confounded by exposure to other chemicals. The only acute exposure animal studies with quantified exposure concentrations of titanium tetrachloride were in rats, and even these were limited. A study investigating the sensory irritation of titanium tetrachloride used a questionable model (Gardner, 1980). The lethality study by Kelly (1980) was specifically designed to evaluate mortality over a wide range of exposure durations. This study was well conducted, and even supplied the individual mortality data and confidence limits associated with the LC_{50} values. However, when using the individual mortality data to calculate the LC_{01} values associated with these exposures, one can see that the animal response varied tremendously depending on the exposure duration. Therefore, although it would be preferable to use the LC_{01} values as an estimate for the lethality threshold, these values were not appropriate. Another limitation of the study was that although the clinical signs and pulmonary histopathological findings were obviously recorded for each group of animals, the severity of the clinical signs and incidence of the pulmonary lesions were not provided for the various exposure concentrations and durations. Therefore, they could not be used as a basis for AEGL derivations. Because of inadequate acute data, an AEGL-1 is not recommended, and the AEGL-2 values are based on repeat-exposure data. The endpoint chosen for the AEGL-2 was essentially a no-adverse-effect level for acute exposure, well below the definition of a defined endpoint for these levels. However, the AEGL-2 values will at least provide a baseline.

Limited genotoxicity studies were available and indicated that titanium tetrachloride is not mutagenic. Carcinogenicity data in humans were limited to a nested case control study that did not find an association between titanium tetrachloride exposure and lung cancer. A two-year carcinogenicity bioassay in rats essentially revealed that the response to chronic inhalation exposure to titanium tetrachloride is consistent with exposure to a dust. However, of uncertain relevance to humans was the finding of squamous cell carcinomas in the area of the alveoli in a few of the high-concentration group rats. Further studies would be needed to address this finding.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, derivation of an AEGL-1 is not recommended.

Derivation of AEGL-2

Key Studies:	Kelly, 1979
Toxicity endpoints:	Rats were exposed to 1.3 ppm for 6 hours/day, 5 days/week for 4 weeks - although no clinical signs reported at this concentration, exposure to the next higher concentration (resulting in labored breathing) approached the lethality threshold concentration.
Time scaling	$C^{0.88} \times t = k$ (this document; based on the LC_{50} values ranging from 2 minutes to 4 hours from Kelly, 1980)
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	none
Calculations:	$(C/\text{Uncertainty Factors})^n \times t = k$ $[(1.3 \text{ ppm})/10]^{0.88} \times 6 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$
<u>10-minute AEGL-2</u>	$C^{0.88} \times 0.167 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$ $C^{0.88} = 5.964 \text{ ppm}$ $C = 7.61 \text{ ppm} = 7.6 \text{ ppm}$
<u>30-minute AEGL-2</u>	$C^{0.88} \times 0.5 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$ $C^{0.88} = 1.992 \text{ ppm}$ $C = 2.19 \text{ ppm} = 2.2 \text{ ppm}$
<u>1-hour AEGL-2</u>	$C^{0.88} \times 1 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$ $C^{0.88} = 0.996 \text{ ppm}$ $C = 0.995 \text{ ppm} = 1.0 \text{ ppm}$
<u>4-hour AEGL-2</u>	$C^{0.88} \times 4 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$ $C^{0.88} = 0.249 \text{ ppm}$ $C = 0.206 \text{ ppm} = 0.21 \text{ ppm}$
<u>8-hour AEGL-2</u>	$C^{0.88} \times 8 \text{ hr} = 0.996 \text{ ppm}^{@}\text{hr}$ $C^{0.88} = 0.125 \text{ ppm}$ $C = 0.0937 \text{ ppm} = 0.094$

Derivation of AEGL-3

Key Studies:	Kelly, 1980
Toxicity endpoint:	1/3 the LC_{50} values
Time scaling	None for the 30, 60, or 240 minute timepoints To extrapolate to 10 and 480 minutes, $C^{0.88} \times t = k$ (this document; based on the LC_{50} values ranging from 2 minutes to 4 hours from Kelly, 1980); the 15-minute LC_{50} value was used to extrapolate to 10 min, the adjusted 240-minute LC_{50} value used to extrapolate to 480 minutes
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	none
Calculations:	$(C/\text{Uncertainty Factors})^n \times t = k$ $[(240 \text{ ppm})/10]^{0.88} \times 0.25 \text{ hr} = 4.10 \text{ ppm}^{\diamond}\text{hr}$ $[(20 \text{ ppm})/10]^{0.88} \times 4 \text{ hr} = 7.36 \text{ ppm}^{\diamond}\text{hr}$
10-minute AEGL-3	$C^{0.88} \times 0.167 \text{ hr} = 4.10 \text{ ppm}^{\diamond}\text{hr}$ $C^1 = 24.55 \text{ ppm}$ $C = 37.98 \text{ ppm} = 38 \text{ ppm}$
30-minute AEGL-3	$130/10 = 13 \text{ ppm}$
1-hour AEGL-3	$57/10 = 5.7 \text{ ppm}$
4-hour AEGL-3	$20/10 = 2.0 \text{ ppm}$
8-hour AEGL-3	$C^{0.88} \times 8 \text{ hr} = 7.36 \text{ ppm}^{\diamond}\text{hr}$ $C^1 = 0.92 \text{ ppm}$ $C = 0.9095 \text{ ppm} = 0.91 \text{ ppm}$

APPENDIX B: Time-Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law (NRC, 1993) or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, these workers showed that the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where n = 1. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

To calculate n for titanium tetrachloride, a regression plot of LC_{50} values was derived using the 2, 5, 15, 30, 60, 120, and 240-minute LC_{50} values determined by Kelly (1980) (13,940; 4600; 713; 390; 171; 143; and 59 ppm, respectively). The LC_{50} values were analyzed using a linear regression analysis of the log-log transformation of a plot of C vs. t to derived a value of n for titanium tetrachloride (see Figure 2).

Linear regression analysis of plot of log-log transformation of plot of C vs. t:

Time	Conc.	Log Time	Log Conc.	Regression Output:	
2	13940	0.3010	4.1443	Intercept	4.3772
5	4600	0.6990	3.6628	Slope	-1.1354
15	713	1.1761	2.8531	R Squared	0.9750
30	390	1.4771	2.5911	Correlation	-0.9874
60	171	1.7782	2.2330	Degrees of Freedom	5
120	143	2.0792	2.1553	Observations	7
240	59	2.3802	1.7709		

n = 0.88

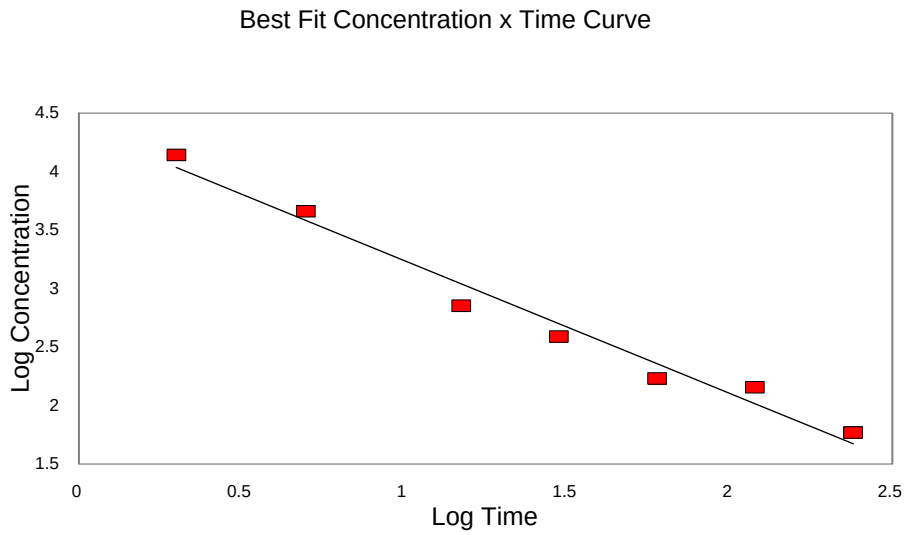

Figure 2. Regression Plot of LC_{50} values: Concentration vs. Time

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APPENDIX C: Derivation Summary for Titanium Tetrachloride AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR TITANIUM TETRACHLORIDE (CAS Reg. No. 7550-45-0) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	**NR**	**NR**	**NR**	**NR**

No acute toxicity data relevant to the definition of an AEGL-1 endpoint are available. Therefore, derivation of an AEGL-1 is not recommended.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
7.6 ppm	**2.2 ppm**	**1.0 ppm**	**0.21 ppm**	**0.094 ppm**

Key Reference: Kelly, D.P. 1979. Four-week inhalation study with titanium tetrachloride (TiCl4). Haskell Laboratory Report No. 459-79, October 1, 1979.

Test Species/Strain/Number: groups of 25 male ChR-CD rats

Exposure Route/Concentrations/Durations: exposed by inhalation to 0.6, 1.3, or 5.2 ppm for 6 h/d, 5 d/wk for 4 wk

Effects:

0.6 ppm	No clinical signs or clinical chemistry changes; increased lung:body weight ratio at terminal kill (increased 126% over controls); histopathology of lungs revealed mild dust-cell reaction
1.3 ppm	No clinical signs; reversible clinical chemistry changes (increased urine pH and decreased urine osmolality); increased lung:body weight ratio at terminal kill and 2 weeks post exposure (136 and 114% of controls, respectively); histopathology changes of acute inflamation of respiratory tract
5.2 ppm	Clinical signs of labored breathing and slightly decreased body weight gain over exposure interval (93% of controls); 2 rats died (test day 15 and 23) from pulmonary damage; clinical chemistry changes (increased urine pH and decreased urine osmolality); increased lung:body weight ratio at terminal kill and 2 weeks post exposure (178 and 128% of controls, respectively); histopathology changes include acute inflamation of respiratory tract

Endpoint/Concentration/Rationale: 1.3 ppm for 6 hours - no clinical signs, but next exposure level approaches lethality threshold

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
Based upon a lack of data identifying interspecies and intraspecies variability, a total uncertainty factor of 100 would normally be applied. However, the endpoint selected (a no adverse-effect level) is below the endpoint defined for the AEGL-2 tier in addition to the fact that the study was a multiple exposure study. Both of these factors make the starting value inherently conservative. Therefore, a total uncertainty factor of 10 was applied.

Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: The value was then scaled across time using the derived value of n=0.88.

Data Adequacy: Data available for titanium tetrachloride AEGL derivations are limited. The only acute human data are case reports of exposures to unknown concentrations or durations. The only animal studies with quantified exposure concentrations of titanium tetrachloride were in rats, and even these were limited. The lethality study by Kelly (1980) was specifically designed to evaluate mortality over a wide range of exposure durations. Although the clinical signs and pulmonary histopathological findings were obviously recorded for each group of animals, the severity of the clinical signs and incidence of the lesions were not provided for the various exposure concentrations and durations. Therefore, they could not be used as a basis for AEGL derivations. Because of inadequate acute data, the AEGL-2 had to be based on a repeat-exposure study. The endpoint chosen for the AEGL-2 was a no-adverse-effect level for an acute exposure, well below the definition of a defined endpoint for an AEGL-2. However, these AEGL values will provide a baseline.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
38 ppm	**13 ppm**	**5.7 ppm**	**2.0 ppm**	**0.91 ppm**

Key Reference: Kelly, D.P. 1980. Acute inhalation studies with titanium tetrachloride. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine; Haskell Laboratory Report No. 658-80, October 31, 1980.

Test Species/Strain/Number: groups of 6 male ChR-CD rats

Exposure Route/Concentrations/Durations: To determine LC_{50} values for various exposure durations, rats were exposed head-only to various concentrations of titanium tetrachloride for 2, 5, 15, 30, 60, 120, or 240 minutes

Effects: Calculated LC_{50} values

duration (min)	LC_{50} value (ppm)
2	13,940
5	4600
15	713
30	390
60	171
120	143
240	59

Endpoint/Concentration/Rationale: to estimate the lethality threshold, the LC_{50} values were divided by 3
One-third calculated LC_{50} values:

duration (min)	⅓ LC_{50} value (ppm)
2	4600
5	1500
15	240
30	130
60	57
120	48
240	20

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 because titanium tetrachloride is an irritant and the mechanism of action is therefore not expected to vary greatly among species. Therefore, a total uncertainty factor of 10 was applied.
Intraspecies: 3 because the mechanism of irritation is also not expected to vary greatly among subpopulations.`

Modifying Factor: none

Animal to Human Dosimetric Adjustment: none

Time Scaling: The adjsuted empirical values for the 30, 60, and 240-minute exposure durations were used for the respective AEGL timepoints. Using an $n = 0.88$, the adjusted 15-minute LC_{50} value was used to extrapolate to 10 minutes, while the adjusted 240-minute LC_{50} value was used to extrapolate to 480 minutes.

Data Adequacy: Data available to derive an AEGL-3 for titanium tetrachloride are very limited. The only acute human data are case reports of exposures to unknown concentrations or durations. The only animal studies with quantified exposure concentrations of titanium tetrachloride are in rat, and even these were limited. The lethality study by Kelly (1980) was specifically designed to evaluate mortality over a wide range of exposure durations. This study was well conducted, and even supplied the individual mortality data and confidence limits associated with the LC_{50} values. However, when using the individual mortality data to calculate the LC_{01} values associated with these exposures, the animals' response varied tremendously depending on the exposure duration. Therefore, although the LC_{01} values would usually be as an estimate for the lethality threshold, these values were not appropriate. Another limitation of the study was that although the clinical signs and pulmonary histopathological findings were obviously recorded for each group of animals, the severity of the clinical signs and incidence of the lesions were not provided for the various exposure concentrations and durations. Therefore, they could not be used as a basis for AEGL derivations.