

TITANIUM (CAS # 7440-32-6)
and
TITANIUM DIOXIDE (CAS # 13463-67-7)

ORAL RISK ASSESSMENT DOCUMENT



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EXECUTIVE SUMMARY

Titanium (CAS # 7440-32-6) and Titanium Dioxide (CAS # 13463-67-7) Oral Risk Assessment			
PARAMETER	Ti LEVEL ¹	UNITS	DERIVED:
NOAEL (no-observed-adverse-effect level)	2,680	mg/kg-day	From a 2-year titanium dioxide feeding study in rats.
Oral RfD (oral reference dose)	3	mg/kg-day	From a 2-year titanium dioxide feeding study in rats.
TAC (total allowable concentration)	90	mg/L	From a 2-year titanium dioxide feeding study in rats, for a 70 kg adult consuming 2 L/day, with a 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	9	mg/L	From the TAC, assuming the default 10 sources of titanium in drinking water.
STEL (short term exposure level)	90	mg/L	Set equal to the TAC.
¹ The solubility of titanium or titanium dioxide in actual use as a direct or indirect drinking water additive should not be exceeded.			
KEY STUDY	NCI (National Cancer Institute). 1978. Bioassay of Titanium Dioxide for Possible Carcinogenicity. NTIS PB288780.		
CRITICAL EFFECT	No significant adverse responses at either of the tested doses		
UNCERTAINTY FACTORS	Uncertainty factors applied in calculating the oral RfD are as follows: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for study duration, since a chronic study was used • 1x for extrapolation from a LOAEL to a NOAEL, since a NOAEL was used • 10x for database deficiencies The total uncertainty factor is, therefore, 1000x.		
TOXICITY SUMMARY	While there are no experimental data by the oral route in humans, titanium is the ninth most abundant element and humans are routinely exposed to it as a natural, direct and indirect food additive. A statistically significant reduction in survival of female mice fed titanium dioxide for two years (NCI, 1978) was of questionable biological significance due to exceptionally high survival of control females, and represented the only significant toxicological effect seen in rats or mice in the 2-year studies. Neoplastic responses to long-term titanium exposure in laboratory animals were observed after high-dose titanium dust inhalation in rats. Those lesions, in addition to the non-neoplastic responses to titanium inhalation exposure in laboratory animals and humans, were attributed to excessive dust accumulation in the lung. Statistically increased neonatal deaths and runts were seen in the second generation of a three-generation reproduction study (Schroeder and Mitchener, 1971), in which rats were exposed to titanium in their drinking water. This study, however, was not conducted according to guidelines and had insufficient experimental detail for use in risk assessment. Titanium compounds did not induce gene mutations in microbial assays or in the mouse lymphoma assay. Titanium dioxide did not induce structural chromosomal aberrations <i>in vitro</i> or <i>in vivo</i>, but did induce micronuclei both <i>in vitro</i> and <i>in vivo</i>, suggesting that it induces micronuclei through chromosome loss (aneuploidy).		
CONCLUSIONS	Based on positive clastogenicity data and negative cancer bioassays in rats and mice, there is <i>inadequate information to assess the carcinogenic potential</i> of titanium and titanium dioxide to humans by the oral route. The concern associated with positive clastogenicity (micronucleus) data is reduced because dietary titanium failed to induce neoplastic lesions following chronic oral exposure in rats or mice. Any significance to the positive micronucleus data or to results of the three-generation reproduction study have been addressed by incorporating appropriate uncertainty factors in the oral risk value calculations. There is limited evidence of carcinogenicity in laboratory animals following inhalation and intramuscular exposure to high levels of titanium dioxide or titanium, but the adverse effects are not considered relevant to drinking water (oral) exposure. It is not appropriate to use the derived oral risk values for titanium tetraiodide, titanium tetrabromide, titanium tetrachloride, titanium tetrafluoride or organotitanium compounds as their chemical, physical, and biological properties differ from those of titanium and titanium dioxide evaluated in this document. Inorganic titanium compounds not specifically excluded are either not manufactured in the United States or have limited available data. Those compounds shall be evaluated on a case-by-case basis to determine whether use of the derived oral risk values is appropriate. The derived TAC, SPAC, and STEL values for titanium and titanium dioxide are protective of public health.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminants **titanium** (leached from mined or natural products, or from titanium alloys) and **titanium dioxide** in drinking water, as extractants from one or more drinking water system components tested under NSF/ANSI 61 (2004), or as contaminants in drinking water treatment chemicals evaluated under NSF/ANSI 60 (2004). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

1.1 NSF Risk Assessment Procedures

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993; U.S. EPA, 2002), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED₁₀ or BMDL from benchmark dose programs) can be used (U.S. EPA, 2003a). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime” (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 2003b).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink 2 liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70 \text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70 \text{ kg}}{2\text{L/day}} \times 0.2 \text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the

estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used. This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.

Finally, a short-term-exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to the TAC or below under static conditions, or to the SPAC or below under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a; U.S. EPA, 1999; U.S. EPA, 2003c; U.S. EPA, 2005). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL to zero, is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10^{-4} to 10^{-6} is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2004) and 61 (2004), the TAC is set at the 10^{-5} risk level, and the SPAC is set at the 10^{-6} risk level. Use of a higher risk level is not ruled out, but would generally require documentation of a benefit to counteract the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2004) and 61 (2004). Application of these values to other exposure scenarios should be done with care, and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation, and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (NRC, 1983) and from the Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a; 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), draft final Guidelines For Carcinogen Risk Assessment (U.S. EPA, 2003c), Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), A Review of the Reference Dose and Reference Concentration Process (U.S. EPA, 2002), Recommendations for and Documentation of Biological Values for

Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (U.S. EPA, 2004).

The literature search strategy employed for these compounds was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- ChemID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Developmental and Reproductive Toxicology (DART)
- TOXLINE – Core and Special
- TRI (Toxics Release Inventory)
- Chemical Carcinogenesis Research Information System (CCRIS)
- Medline (via PubMed)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)
- Current Contents (as requested)

1.2 Scope of This Document

It is not appropriate to use the oral risk values derived in this document for titanium tetraiodide, titanium tetrabromide, titanium tetrachloride, titanium tetrafluoride or organotitanium compounds as their chemical, physical, and biological properties differ from those of titanium and titanium dioxide. Inorganic titanium compounds not specifically excluded are either not manufactured in the United States or have limited available data. These compounds shall be evaluated on a case-by-case basis to determine whether use of the derived oral risk values is appropriate.

The World Health Organization (WHO) published Environmental Health Criteria 24 on titanium in 1982, and much of the available toxicological information has been reviewed in that document. Only those studies not included in the WHO (1982) document were acquired by NSF for review, unless it was believed that obtaining a previously reviewed study would contribute significantly to this risk assessment. The WHO (1982) document is available online at <http://www.inchem.org/documents/ehc/ehc/ehc24.htm>.

The literature search for titanium was conducted on August 16, 2004 and the literature search for titanium dioxide was conducted on August 18, 2004. This document includes relevant information retrieved as a result of those searches that was not included in the WHO (1982) document. However, the extensive body of literature on use of titanium and titanium alloys in medical implants or dental alloys was not reviewed for this document. While illustrating the low toxicity of titanium, findings in these studies generally focused on performance and either were not relevant to oral risk assessment or did not include quantitative exposure and/or response data. A second extensive body of literature covering occupational exposure to inhaled titanium dusts

and fumes was not fully reviewed, as findings were not considered relevant to oral risk assessment.

2.0 PHYSICAL AND CHEMICAL PROPERTIES

Titanium is a metallic element with the symbol Ti. Titanium dioxide is an inorganic oxide with the formula TiO_2 . The chemical and physical properties of titanium are listed in Table 1, and the chemical and physical properties of titanium dioxide are listed in Table 2.

Table 1. The physical and chemical properties of titanium

Property	Data	Reference
Empirical Formula	Ti	HSDB, 2004
CAS#	7440-32-6	HSDB, 2004
Molecular Weight	47.90	HSDB, 2004
Physical State and Color	Solid grey metal	WHO, 1982
Melting Point	1660 °C	Weast, 1988
Boiling Point	3287 °C	Weast, 1988
Density	4.5 at 20 °C	Weast, 1988
Vapor Pressure	Not applicable	
Water Solubility	Insoluble	Chemfinder, 2004
pK _a	Not applicable	
n-Octanol/Water Partition Coefficient (log K _{ow})	Not located	
Henry's Law Constant (air/water partition)	Not applicable	

Table 2. The physical and chemical properties of titanium dioxide

Property	Data	Reference
Empirical Formula	TiO_2	HSDB, 2004
CAS#	13463-67-7	HSDB, 2004
Molecular Weight	79.90	HSDB, 2004
Physical State and Color	Crystals or powder, white	HSDB, 2004
Melting Point	1855 °C 1843 °C	Chemfinder, 2004 HSDB, 2004
Boiling Point	2900 °C, 2500-3000 °C	Chemfinder, 2004 HSDB, 2004
Density	4.26 4.23	Chemfinder, 2004 HSDB, 2004
Vapor Pressure	Not applicable	
Water Solubility	Insoluble. < 0.1 g/100 mL at 20 °C Insoluble	Chemfinder, 2004 HSDB, 2004
pK _a	Not applicable	
n-Octanol/Water Partition Coefficient (log K _{ow})	Not located	
Henry's Law Constant (air/water partition)	Not applicable	

2.1 Unique Properties

Titanium exists in three oxidation states, +4, +3, and +2, of which the +4 state is the most common. The metal is the ninth most abundant element in the earth's crust and occurs in both cationic (titanium chlorides, phosphates and sulfates) and anionic (calcium, iron and sodium titanates) states (WHO, 1982). Titanium has a great affinity for oxygen, nitrogen and moisture in the air, and consequently does not exist in the metallic state in nature. Rather, titanium is typically found in the form of stable minerals or impurities (WHO, 1982). It is most commonly found as part of the mineral ilmenite (FeTiO_3) or as one of three different crystal lattices: rutile, anatase, or brookite (Lee et al., 1985).

2.2 Organoleptic Properties

Very little information on the organoleptic properties of titanium and its associated compounds has been reported in the literature. Titanium dioxide has been described as a tasteless powder (WHO, 1982), and as tasteless and odorless (HSDB, 2004).

3.0 PRODUCTION AND USE

3.1 Production

Titanium is mined commercially from rock and sand deposits (WHO, 1982). Titanium metal, known as “sponge” metal, is produced principally by the Kroll process, which involves reduction of titanium tetrachloride with magnesium metal to yield titanium alloy of 99.5% purity. Similarly, the sponge metal can be produced by the reduction of titanium tetrachloride with sodium metal (Hunter process). Titanium metal powder is typically produced by reacting the metal with hydrogen, forming a brittle titanium hydride that is further processed to remove the hydrogen.

Between 8,000 and 16,000 tons of titanium sponge metal and between 1.2 and 1.4 million tons of titanium dioxide were produced in the United States between 1996 and 2000 (U.S. Geological Survey, 2001). The annual production of titanium in the United States was 22,000 tons in 1985, and the total world production of titanium and titanium dioxide in 2000 was approximately 4.5 million tons (U.S. Geological Survey, 2001). The major producers of titanium and titanium dioxide in 2000 were the United States, China, Japan, Kazakhstan, Russia, and Ukraine.

3.2 Use

A 2000 estimate reports that 60% of titanium was used in aerospace applications (U.S. Geological Survey, 2001). The remaining 40% had applications in the armor, chemical processing, power generation, marine, medical, and sporting goods industries.

Beneficial qualities of titanium include its strength and corrosion resistance. The vast majority of titanium metal is employed in aerospace applications, as titanium is as strong as steel, but is 45% lighter. Its ability to resist strong acids, sulfides and bleaches has led to the development of titanium-containing tubing and liners used in the paper pulp industry and in chemical and

electrochemical processing industries. These same properties have allowed for the development of surgical implants and prostheses, in which titanium is a component (Friberg et al., 1986).

Of the titanium-containing compounds, titanium dioxide is by far the most commercially important. Titanium dioxide is used extensively in paints, lacquers and enamels because of its extreme whiteness and its high index of refraction. A 1982 estimate suggested that greater than half of all white or light-colored coatings contained titanium dioxide (WHO, 1982). These same brightening qualities of titanium dioxide have resulted in its use in the paper industry to improve the brightness of paper coatings and fillers. The fastest growing application of titanium dioxide is in the plastics industry, where it is valued for its whiteness, resistance to degradation, high refractive index, and inertness (WHO, 1982).

Titanium dioxide meeting the required specifications in the U.S. Code of Federal Regulations, Title 21 (U.S. FDA, 2004; Food Chemical News Guide, 2002) may be used as a direct additive in foods (Section 73.575), drugs (Section 73.1575), cosmetics (Section 73.2575), and medical devices (Section 73.3126). It may also be used in over-the-counter sunscreen drug products (U.S. FDA, 1999). As an indirect additive, titanium dioxide is prior-sanctioned per Section 181.30 under substances used in the manufacture of paper and paperboard products used in food packaging; and is also sanctioned for use, generally as a colorant or filler, in a variety of food contact articles including adhesives, coatings, and polymers (U.S. FDA, 2004). Titanium dioxide has also been accepted for use as a marker in meat products (1%) and as a food pigment in meat and cheese spreads ($\leq 0.5\%$).

Primarily an intermediate in titanium metal production, titanium tetrachloride is also used as a catalyst in the polymerization of ethylene, propylene, and several other hydrocarbons, and serves as the primary raw material for most organic titanium compounds. The majority of the organotitanium compounds produced are in the form of alkyl and aryl titanates. These compounds are principally used as cross-linking agents and catalysts. A more complex organic compound, titanocene dichloride $[(C_5H_5)_2TiCl_2]$, has been studied as a potential antitumor agent (WHO, 1982).

4.0 ANALYTICAL METHODS

Titanium compounds have been analyzed in water, food, and air by a variety of methods including anion exchange, colorimetric, X-ray fluorescence, atomic absorption, and mass spectrometric techniques. The latter two methods require volatilization/atomization of the sample.

4.1 Analysis in Water

Titanium, like many trace metals, can be determined analytically in water by x-ray fluorescence and/or ion exchange. More often, it is analyzed using inductively coupled plasma atomization or ionization followed by atomic absorption or mass spectrometric detection (WHO, 1982; HSDB, 2004). NSF uses an inductively coupled plasma mass spectrometry method for the analysis of titanium in water. The method detection limit is 0.002 mg/L.

4.2 Analysis in Biological Matrices

Titanium is typically determined in biological samples by spectroscopic or photometric techniques (WHO, 1982; HSDB, 2004). Specifically, titanium in human foods and excreta has been analyzed by arc emission spectroscopy, electron probe microanalysis, mass spectrometry and X-ray fluorescence. Detection limits by these methods range from 0.005 to 10 mg/kg.

Titanium is most commonly determined in food by spectroscopic and colorimetric techniques (WHO, 1982; HSDB, 2004). Titanium dioxide is determined in cheese by the Kolthoff and Sandell method, by which reaction products generated as a result of treating titanium solutions with hydrogen peroxide are measured spectrophotometrically. Canned fruit and vegetable juices are analyzed for titanium by emission spectroscopy. Spark-source mass spectrometry and x-ray fluorescence methods have been developed to measure titanium and other elements in prepared diets.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

Food is the main source of exposure to titanium for the general population (WHO, 1982). In 1963, the typical American diet was estimated to include approximately 300 µg titanium/day. A 1972 estimate of 540 µg titanium/day was reported for the United Kingdom. Large variations in titanium concentration have been reported in food. While some foods contain little or no detectable titanium, other foods, such as milled grains, butter, corn oil, margarine, and lettuce have higher levels (1.76-2.42 mg/kg). Levels higher than those in this range have been detected in foods containing or those processed with titanium dioxide, although the exact concentrations have not been documented. In a study of dietary microparticles, Lomer et al. (2004) estimated that the median dietary intake of titanium dioxide was 2.5 mg per individual per day.

Both titanium and titanium dioxide have applications in cosmetics and medicine. Titanium dioxide is used as an ultraviolet absorbing ingredient in sunscreens (Brand et al., 2003), in herpes simplex treatments and in anti-acne ointments, and for cosmetic treatment of hemangiomas. Titanium alloys are increasingly used as implant materials in orthopedics, oral surgery and neurosurgery.

Titanium has also been detected in municipal water supplies, where 81% of evaluated water supplies in the United States in 1964 contained a mean concentration of 2.1 µg/L titanium (WHO, 1982).

Occupationally, workers can be exposed to titanium dusts, fumes and vapors, mainly through mining, production, or processing of the metal and its related compounds. Air concentrations in some occupational settings have been reported as high as 50 mg/m³ (Kazantzis, 1981).

5.2 Sources of Environmental Exposure

Titanium has been detected frequently in natural water supplies at concentrations ranging from 2-107 µg/L. Titanium dioxide with ultraviolet photocatalysis, using chlorine as a secondary disinfectant, has been studied for use in small drinking water systems (Richardson et al., 1996). One unique byproduct, tentatively identified as dihydro-4,5-dichloro-2(3*H*)furanone was identified from this process. Titanium dioxide combined with ultraviolet irradiation has also been tested in advanced oxidation processes to produce hydroxyl radicals used to pre-treat or treat wastewater from tannery (Schrank et al., 2004) or dyeing (Lee et al., 2005) operations. Titanium ambient air concentrations are greatest in urban areas, but are typically lower than 0.1 µg/m³. Soil concentrations vary widely, but average at or below 5 g/kg (WHO, 1982).

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

Absorption of titanium from the gastrointestinal tract is implied by some excretion in the urine of humans and laboratory animals. Quantitative oral data are lacking. Limited information suggests widespread distribution of titanium in the body, without appreciable accumulation. Most ingested titanium is excreted in feces.

6.1 Absorption

Data on the oral absorption of titanium in humans are not available, and the suggestion that titanium can be absorbed from the gastrointestinal tract is inferred from the available animal data. Titanium in man was reported to accumulate with age only in the lungs (ICRP, 1959 as cited in WHO, 1982). Skin penetration of titanium dioxide reportedly did not occur (ECB, 2000).

Data in laboratory animals suggest that ingested titanium is absorbed to some extent from the gastrointestinal tract (WHO, 1982). Lloyd (1955, as cited in WHO, 1982) examined the digestibility of titanium and reported that 92% of titanium dioxide fed to rats at 2.5 g/kg was recovered, but provided little explanation for the remainder of the administered dose. In a study in which mice were administered ⁴⁴Ti intragastrically, the whole body count taken 24 hours after dosing did not exceed background (Thomas and Archuleta, 1980 as cited in WHO, 1982).

6.2 Distribution

A wide range of titanium concentrations has been detected in human tissues, with the highest concentrations most frequently reported in the lungs. Detectable concentrations of titanium were observed in study subjects by the third decade, while titanium was not found to accumulate in the kidney, skin or aorta at the same age (Schroeder, 1963 as cited in WHO, 1982). Titanium has also been detected in the tissues of newborn infants, suggesting transplacental titanium transfer (WHO, 1982). Blood concentrations of titanium range from 0.02-0.123 mg/L in healthy study subjects (Hamilton, 1972; Maillard and Ettori, 1936; and Timakin, 1967 as cited in WHO, 1982).

Following a 32-day feeding study with titanium dioxide (100,000 mg/kg), titanium was retained only in unspecified muscles of treated male and female rats, at 0.06 and 0.11 mg/kg, respectively. Titanium failed to accumulate in the liver, spleen, kidney, bone, plasma or erythrocytes in the same animals (West and Wyzan, 1963 as cited in WHO, 1982). Following oral exposure to 0 or 5 mg/L titanium potassium oxalate for the lifetime of the study mice, nearly identical concentrations of titanium were observed in the heart (~ 7 mg/kg), lungs (~ 4 mg/kg), spleen (~ 7 mg/kg), liver (~ 3 mg/kg) and kidneys (~ 2 mg/kg) of treated laboratory mice, and in wild field mice collected for comparison. However, untreated laboratory mice presented with much lower levels of titanium in their tissues than either the treated laboratory or wild field mice, especially the males (Schroeder, 1964 as cited in WHO, 1982).

Fifteen minutes after intravenous injection of 250 mg/kg titanium dioxide nearly 80% of the dose was found in the liver. After six hours, the highest concentration remained in the liver and the next-highest concentration was found in the spleen. However, by 24 hours and through a full year after exposure, the highest concentration of titanium was detected in the celiac lymph nodes (Huggins and Froehlich, 1966 as cited in WHO, 1982).

6.3 Metabolism

The vast majority of ingested titanium is excreted unchanged in feces (WHO, 1982). The metabolism, if any, of systemically absorbed titanium has not been discussed in the reviewed literature.

6.4 Elimination/Excretion

The concentration of titanium in human urine was reported to be approximately 0.01 mg/L (Perry and Perry, 1959 as cited in WHO, 1982). It is unclear in the WHO document whether the data are representative of environmental exposure or are the result of controlled study. Higher titanium concentrations (0.41-0.46 mg/L) have been reported in human urine (Tipton, 1961 as cited in WHO, 1982). Most ingested titanium is excreted in feces (WHO, 1982). Titanium accumulation has been reported in the lungs, and two estimates of biological half-lives in man of 320 and 640 days have been made (ICRP, 1959 as cited in WHO, 1982).

No data were reported in the literature on the clearance of titanium following oral exposure in laboratory animals. Radioactive titanium had a mean biological half-life of 640 days in mice when administered by the intraperitoneal and intravenous routes (Thomas and Archuleta, 1980 as cited in WHO, 1982). Following inhalation of 15 mg/m³ titanium dioxide in rats (assuming constant 24 hour exposure, ~ 20 mg/kg-day TiO₂ or 12 mg/kg-day Ti), approximately 40-45% of the deposited particles were cleared from the lungs in 25 days (Ferin and Feldstein, 1978 as cited in WHO, 1982). The clearance rate decreased significantly, however, following exposure to 100 mg/m³ (~ 145 mg/kg-day TiO₂ or 85 mg/kg-day Ti). Similar clearance rates were reported following intratracheal administration. Additional detail on the study design and results was not provided by WHO (1982), and no clearance mechanism was discussed.