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Environmental Health Criteria 24

TITANIUM

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

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ENVIRONMENTAL HEALTH CRITERIA FOR TITANIUM

Further to the recommendations of the Stockholm United Nations Conference on the Human Environment in 1972, and in response to a number of World Health Assembly resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68) and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

The first draft of the present document was prepared by Dr L. Fishbein, National Center for Toxicological Research, US Food and Drug Administration, Jefferson, AZ, USA. The draft was reviewed by the Task Group on Environmental Health Criteria for Titanium and then revised and updated by Dr H. Nordman, Institute of Occupational Health, Helsinki, Finland. Finally, the revised document was circulated to the members of the Task Group for their comments, in March 1982.

The Secretariat wishes to thank Dr H. Nordman for his help in the preparation and scientific editing of the final draft.

The document is based primarily on original publications listed in the reference section. However, several publications reviewing the health effects of titanium have also been used. These include reviews by Berlin & Nordman (1979), Browning (1969), CEC (1974), Katari et al. (1977), Lynd & Hough (1980), Schroeder et al. (1963), Stamper (1970), Stokinger (1963), US EPA (1973), Valentin & Schaller (1980), and Vinogradov (1959).

Details of the WHO Environmental Health Criteria Programme, including definitions of some of the terms used in the documents, may be found in the general introduction to the Environmental Health Criteria Programme, published together with the environmental health criteria document on mercury (Environmental Health Criteria 1 - Mercury, Geneva, World Health Organization, 1976) and now available as a reprint.

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1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

1.1 Summary

1.1.1 Properties and analytical methods

Titanium is a grey metal with an atomic number of 22 and a relative atomic mass of 47.9. It is extremely resistant to corrosion and, in the form of a powder or dust, is highly flammable and explosive. The most common oxidation state of titanium is +4, but +3 and +2 states also exist. Titanium occurs in both a cationic state (e.g., titanium chlorides, phosphates, and sulfates) and an anionic state (e.g., calcium, iron, and sodium titanates). Metallic titanium, titanium dioxide, and titanium tetrachloride are the compounds most widely used in industry.

A wide variety of analytical methods has been used for the determination of titanium in various media. Spectrographic and photometric methods have been employed for the determination of titanium in food and water. X-ray fluorescence and neutron activation analysis have been widely used for the measurement of titanium in air. Spark-source mass spectrography has been used to determine titanium in biological samples, food, and water. Titanium does not easily atomize and has a tendency to form refractory oxides, which may influence the use of atomic absorption assays. The detection limit for titanium in air using atomic absorption spectrophotometry (AAS) is about 0.07 $\mu g/m^3$. Using X-ray fluorescence for the determination of titanium in air, a detection limit of 0.011 $\mu g/m^3$ can be achieved; for human tissues, a detection limit of 0.3 mg/kg has been reported. Proton-induced X-ray emission spectrometry can be used for the determination of titanium in air and water.

1.1.2 Sources and uses

Titanium, the ninth most abundant element in the earth's crust, is widely distributed. Metallic titanium is mainly used in the aircraft industry and in the production of high-strength, corrosion-resistant alloys. It is also used in the chemical industry as a lining material, because of its corrosion-resistant properties. Titanium dioxide is extensively used as a white pigment in paints, enamels, plastics, and cosmetics as well as a colouring agent in food. Titanium carbide is important in the production of cutting tools. Titanium tetrachloride is the common intermediate in the production of titanium catalysts and is also used for the synthesis of organic titanium compounds. Smaller amounts of titanium compounds are used in the electrical and dyeing industries.

The main sources of contamination of the general environment with titanium are the combustion of fossil fuels and the incineration of titanium-containing wastes. In occupational settings, exposure mainly occurs during the processing of titanium-containing minerals, metallic titanium, and titanium dioxide.

1.1.3 Environmental levels and exposures

Owing to its great affinity for oxygen and other elements, titanium does not exist in the metallic state in nature. The average concentration in the earth's crust is 4400 mg/kg. Titanium concentrations in the urban air are mostly below 0.1 μg/m^3, though levels exceeding 1.0 μg/m^3 have been reported, especially in industrialized areas. In rural air, concentrations are still lower. In working environments, the air concentration may reach several mg/m^3. The titanium concentration in drinking-water supplies is generally low, having an approximate range of 0.5-15 μg/litre. Large variations in the concentrations of titanium in different types of foods have been reported. A typical diet may contribute some 300-400 μg/day, but higher intakes ranging up to 2 mg per day have been reported.

1.1.4 Chemobiokinetics and metabolism

Quantitative information on absorption through inhalation is lacking. Absorption of titanium from the gastrointestinal tract takes place, but the extent of this absorption is not known. Based on average titanium concentrations found in human urine of about 10 μg/litre, it can be calculated that the absorption is about 3%, assuming a daily intake of at least 500 μg.

The highest concentrations of titanium have usually been found in the lungs, followed by the kidney and liver. In most studies on concentrations of titanium in blood, levels reported have been about 0.02-0.07 mg/litre. Titanium crosses the blood-brain barrier and is also transported through the placenta into the fetus. It seems to accumulate with age in the lungs, but not in other organs. In the two reports available, the biological half-life for titanium in man has been calculated to be about 320 days and 640 days, respectively.

Most ingested titanium is eliminated unabsorbed. In man, titanium is probably excreted with urine at an approximate average rate of 10 µg/litre. Excretion by other routes is unknown.

1.1.5 Effects on experimental animals and man

There is no evidence of titanium being an essential element for man or animals.

Studies on experimental animals as well as human clinical studies have shown that titanium in implants and prostheses is extremely well tolerated by osseous and soft tissues. This is shown by lack of irritation, normal wound-healing, and encapsulation of the metal by fibrous tissues. Titanium dioxide, salicylate, oxide, and tannate have been used in various dermatological and cosmetic formulations, without any known adverse effects. However, exposure to different titanium compounds appears to induce various levels of slight pulmonary fibrosis.

Titanium dioxide is a frequently used compound in lung clearance studies, where a biologically inert substance is required. Acute and subacute toxicity studies have not shown any detrimental effects of titanium dioxide in the lungs. In some experimental studies in which rats and guinea-pigs were exposed to titanium dioxide dusts, slight fibrosis was occasionally found in the lung tissue. However, the exposure in these studies was not to pure titanium dioxide and a possible explanation for the fibrogenic activity may be concomitant exposure to other elements, such as silica (SiO_2). Autopsy studies on workers exposed to titanium dioxide for long periods have not shown any evidence of fibrogenic activity. This is consistent with the few epidemiological surveys made on working populations exposed to titanium dioxide dusts. In one report, slight fibrosis was observed, but this may have been due to the coating material containing aluminium silicate rather than the titanium dioxide.

In studies on rats, intratracheal administration of 50 mg of titanium nitride induced a weak fibrogenic effect after 6 months. Slight fibrosis was detected in similar studies in which rats were exposed to titanium hydride, boride, or carbide. Data on the exposure of man to such titanium compounds are lacking.

Results of long-term toxicity studies showed that titanium, in the form of a soluble salt, administered to mice in the drinking-water at a concentration of 5 mg Ti/litre from weaning to natural death, did not significantly affect life span. Feeding technical grade titanium dioxide to guinea-pigs (0.6 g/day), rabbits (3 g/day), cats (3 g/day), and one dog (9 g/day) for 390 days did not cause any adverse effects in the animals. Few data exist on the systemic effects of titanium and its compounds. Intratracheal administration of 50 mg of titanium hydride to rats induced dystrophic changes in the myocardium, liver, and kidneys. Similar effects were seen after administration of titanium boride or carbide to rats.

A dose-related mortality rate was found in mice exposed to hydrolytic products of titanium tetrachloride through inhalation for 2 h (titanium compounds plus hydrochloric acid).

Accidental splashing of workers with titanium tetrachloride and exposure to aerosols of titanic acid and titanic oxychloride led to skin burns with scarring, and congestion of the mucosa in the upper respiratory tract, followed later by cicatrization and laryngeal stenosis. Accidental exposure to liquid titanium tetrachloride, which was then washed off, resulted in severe burning of the skin, due to an exothermic reaction between the titanium tetrachloride and water.

The only carcinogenic effect of titanium, so far reported, consisted of the development of fibrosarcomas at the site of injection in rats injected with either titanium metal or titanocene suspended in trioctanoin.

In a 3-generation study on rats, titanium potassium oxalate (5 mg/litre) in the drinking-water caused a marked reduction in the numbers of animals surviving to the third generation.

1.1.6 Evaluation of health risks

Titanium compounds are poorly absorbed from the gastrointestinal tract, which is the main route of exposure for the general population. Available data on the occurrence of titanium and titanium compounds in the environment, as well as data on toxicity, indicate that the current level of exposure of the general population does not present a health risk. In the occupational environment, exposure occurs through inhalation and titanium is retained in the lungs. Dose-effect and dose-response relationships have not yet been established for any of the effects of various titanium compounds.

Titanium metal in surgical implants is well tolerated by tissues and titanium compounds, such as titanium dioxide, salicylate, and tannate, have been used in cosmetics and in pharmaceutical and food products, without any reported adverse effects.

A variety of animal and human studies have shown that inhaled titanium dioxide is biologically inert. Weak fibrosis, found in association with exposure to various titanium dusts, is likely to be due to concomitant exposure to other components rather than to the titanium dioxide.

According to animal studies, titanium nitride, hydride, carbide, and boride may have fibrogenic effects. These compounds have also been observed to cause liver and kidney dystrophy. Titanium tetrachloride causes skin burns and is strongly irritant to mucous membranes and the eyes. Powdered titanium metal may induce fibrosarcomas and lymphosarcomas in rats, when injected intramuscularly, but there is no evidence of titanium being carcinogenic in man.

Administration of a soluble titanate disturbed reproduction in a 3-generation study on rats. Teratogenic effects of titanium have not been reported.

1.2 Recommendations for Further Studies

There is not sufficient information available on titanium, to estimate the actual exposure of the general population from all environmental media. Dose-effect and dose-response relationships have not been established and it is therefore proposed that more information be generated to cover the following aspects:

(a) environmental aspects; size distribution of particles in ambient and occupational environments;
(b) metabolic aspects; balance studies including metabolic mechanisms;
(c) toxicological aspects; effects of various types of titanium dust, taking into account differences in crystal lattices; effects of titanium compounds such as the nitride, hydride, boride, and carbide in short- and long-term studies;
(d) occupational aspects; effects of exposure to titanium tetrachloride and organotitanium compounds.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Chemical and Physical Properties

Titanium (atomic number 22; relative atomic mass 47.90; density 4.507 g/cm^3 at 20 °C) is a silvery grey metal in group IV of the periodic table and is a member of the first transition series of elements. Titanium has both metallic and non-metallic characteristics. Its most common oxidation state is +4 (titanic compounds), but +3 (titanous compounds) and +2 forms are also known, in addition to oxy forms such as titanyl chloride ($TiOCl_2$). The metallic characteristics of titanium are shown in compounds such as titanium chloride, phosphate, sulfate, and nitrate, whereas the non-metallic characteristics are exhibited in a series of titanates, e.g., calcium, iron, and sodium titanates. Titanium(IV) compounds are easily hydrolysed into titanium dioxide (Stamper, 1970; ACGIH, 1973; Weast, 1980).

Table 1. Some physical and chemical data on titanium and selected titanium compounds[a]

Compound	Melting point (°C)	Boiling point (°C)	Solubility	
			Soluble	Insoluble
Titanium (Ti)	1660±10	3297	dilute acids	cold & hot water
- dioxide (TiO_2)	1830-1850	2500-3000	alkalies, sulfuric acid	cold & hot water
- tetrachloride ($TiCl_4$)	-25	136.4	cold water, alcohol, dilute hydrochloric acid	decomposes in hot water
- sulfate ($Ti[SO_4]_3$)			diluted acids	cold & hot water, alcohol, ether
- carbide (TiC)	3140±90	4820	aqua regia, nitric acid	cold & hot water

[a] Adapted from: Weast (1980).

The metal is highly resistant to corrosion by many agents including concentrated nitric acid, 5% sulfuric acid, and sea water. Titanium powders are highly pyrophoric and molten titanium burns in air. Thus, an explosion hazard is associated with the production of the metal. Titanium and its alloys may react strongly with oxidizing agents, especially when in the form of powdered metal (Mogilevskaja, 1972; ACGIH, 1973). Titanium dioxide (TiO_2) is a white, tasteless powder. It exists in three crystalline forms; anatase, brookite, and rutile.

Titanium tetrachloride is a liquid, which is stable in dry air, but decomposes in cold water to form titanium oxide and hydrochloric acid. The physical and chemical properties of titanium and some of its compounds are listed in Table 1 (Stamper, 1970; Weast, 1980).

A large number of organotitanium compounds are known. The most common types are the alkyl and aryl titanates of the general formula $Ti(OR)_4$. In addition, there are complex organic compounds of titanium such as titanocene. Titanium has an atomic radius similar to, and thus is capable of substitution for, other transitional metals, e.g., vanadium, iron, cobalt, nickel, and zinc (Barksdale, 1966; Stamper, 1970; Katari et al., 1977).

2.2 Analytical Methods

A wide variety of analytical procedures has been used for the determination of titanium in various media. Spectrographic and photometric methods have been employed for the determination of titanium in food and water. X-ray fluorescence has been widely used for the determination of titanium in air. Neutron activation analysis has been employed to estimate titanium levels in air and spark-source mass spectrography to determine titanium concentrations in biological samples, food, and water.

Atomic absorption spectroscopy (AAS) is the generally preferred method for the determination of trace elements. However, titanium is not easily atomized in flame media and has a tendency to form refractory oxides, which detracts from the usefulness of atomic absorption assays. Nevertheless, a variety of atomic absorption techniques has been reported using high-temperature reducing flames such as the nitrous oxide-acetylene flame (Kirkbright et al., 1969). Slavin & Manning (1963) achieved a sensitivity of 12 mg/litre (1% absorption) when determining titanium in an alcohol solution. In order to obtain a higher sensitivity, indirect atomic absorption techniques have been developed. The sensitivity obtainable in the AAS determination of molybdenum being higher than that of titanium, Kirkbright et al. (1969) used the molybdenum-titanium ratio (11:2) in molybdotitanophosphoric acid. The sensitivity obtained at 1% absorption was 0.0013 mg/litre. An indirect method reported by Ottaway et al. (1970) is based on the enhancement of the atomic absorption signal of iron by titanium. This method is suitable for the determination of titanium in concentrations of 0.01-10 mg/litre. Suppression of the absorbance of strontium by titanium was used by Chakrabarti & Katyal (1971) in an assay with which it was possible to determine titanium in concentrations of 0.2-10 mg/litre. Atomic absorption spectrometry for the determination of titanium in pharmaceutical products has been reported by Mason (1980).

Potentiometric and photometric methods of titration have been reported for the determination of titanium but most of these methods are not very sensitive (Škaravskij, 1965; Ozawa, 1971).

2.2.1 Air analysis

The determination of trace metal particulates, including titanium, in atmospheric samples by X-ray fluorescence (XRF) techniques has been widely reported (National Air Pollution Control Administration, 1969; Shono & Shinra, 1969; Dittrich & Cothern, 1971; Frigieri et al., 1972; Rhodes et al., 1972). For example, trace metals collected on filter paper by a high volume air sampler for 25 h were analysed by Dittrich & Cothern (1971) using the XRF technique. Elements in the periodic table between titanium and caesium were found to have a sensitivity limit of 0.5 $\mu g/m^3$ of air. The XRF technique has the advantage of being non-destructive, and a single analysis provides simultaneous estimates of several metals. The method can be easily automated.

Rhodes et al. (1972) measured titanium among other elements in samples of suspended particulate matter, collected in 38 air quality control network stations in Texas. The X-ray fluorescence method proved useful for air particulate survey measurements and for pollution source location. No sample preparation was necessary. Once loaded with samples, the apparatus could operate unattended. The detection limit of XRF for titanium was 0.011 $\mu g/m^3$. In an analytical study described by Giauque et al. (1974), sensitivities routinely established within a 20-min counting interval corresponded to less than 0.01 $\mu g/m^3$ of air.

Non-destructive neutron activation analysis has also been used for the determination of trace elements in aerosols (Dams et al., 1970, 1972; Zoller & Gordon, 1970; Harrison et al., 1971). The multi-elemental specificity of activation analysis aids in the determination of the chemically complex and highly variable composition of an aerosol. A useful irradiation-counting scheme and simplified flow diagram of automated spectrum analysis has been developed by Dams et al. (1970) with detection limits for titanium of the order of 0.2 μg.

Most techniques in which neutron activation analysis is used require a large nuclear reactor, with the minimum flux for best overall performance acknowledged to be around 10^{12} neutrons/second per cm^2. However, it was suggested by Dittrich & Cothern (1971) that the future availability of californium $(^{252}Cf^{5})$ should provide adequate portable activation sources for atmospheric trace metal analysis.

The determination of a variety of metals in atmospheric particulate matter by atomic absorption spectroscopic (AAS) procedures has also been widely reported (Beyer, 1969; Burnham et al., 1970; Ranweiler & Moyers, 1974). Ranweiler & Moyers (1974) described an AAS procedure for the determination of 22 metals including titanium in 24-h, high-volume samples of atmospheric particulate matter collected on a polystyrene filter. The practical detection limit for titanium was 0.07 $\mu g/m^3$.

Johansson et al. (1975) used proton X-ray emission spectroscopy for the determination of titanium and 13 other elements in airborne particles. In this method, particles were collected and segregated according to size, using cascade impactors.

2.2.2 Water analysis

The determination of trace metals, including titanium, in water has been accomplished principally by X-ray fluorescence (Blasius et al., 1972), spectrography (Durum & Haffty, 1961), spark-source mass spectrophotometric (Crocker & Merritt, 1972; Hamilton & Minski, 1972), and photometric techniques (Nikitina & Basargin, 1970). Elements in the periodic table between titanium and caesium were detectable by X-ray fluorescence with sensitivities of the order of 30 μg/kg for metals in the particulate form and 0.4 μg/kg for metals in the ionic form (Blasius et al., 1972).

Problems with the XRF technique are primarily concerned with sample preparation and matrix effects. However, the most important need defined by Blasius et al. (1972) was the determination of the chemical and/or the physical form in which the metal occurred. It appeared that some of the metals were in the suspended state, while the rest were either ionized or attached to colloidal particles.

Proton-induced X-ray emission spectrometry has been used for the determination of titanium in water (Johansson, 1974; Johansson et al., 1975).

Crocker & Merrit (1972) and Hamilton & Minski (1972) used spark-source mass spectroscopy for the determination of trace elements, including titanium, in water. A selective and sensitive photometric method employing tichromin was developed by Nikitina & Basargin (1970) for the determination of 0.1 mg titanium/litre in highly mineralized thermal waters of volcanic origin.

2.2.3 Food analysis

Titanium levels in various food sources have mainly been determined by spectrographic and colorimetric techniques. Emission spectrum analysis has been used for the determination of titanium in canned fruit and vegetable juices (Klyačko et al., 1971, 1972). The determination of titanium dioxide in cheese was accomplished by Leone (1973) using the procedure of Kolthoff & Sandell (1952) in which titanium solutions are treated with hydrogen peroxide and the resulting yellow-orange colour due to $(TiO_2(SO_4)_2)$ is measured spectrophotometrically.

The occurrence of titanium together with a large number of other chemical elements in samples of prepared diets from the United Kingdom and the possible relationship with environmental factors has been determined by Hamilton & Minski (1972/1973) using spark-source mass spectrometry (Hamilton et al. 1972/1973; Hamilton & Minski, 1972/1973) and X-ray fluorescence (Hamilton et al., 1972/1973).

2.2.4 Analysis of biological materials

Titanium in biological samples has mainly been determined by photometric (Lojko, 1967; Urusova, 1969; Mal'ceva, 1973a,b) and spectroscopic (Timakin & Bagdasarova, 1969; Čekotilo & Torohtin, 1970) techniques. Mal'ceva (1973a,b) determined titanium in ashed bone samples with a detection limit of 0.16 mg/kg of bone tissue, or 350 µg/kg of biological material or litre of urine.

Titanium in tissues was measured by Schroeder et al. (1963) using chromotropic acid in a colorimetric microanalytical technique of Sandell (1959). The method was sensitive to about 0.025 mg/kg. A colorimetric method using the sodium salt of chromotropic acid was used for the determination of titanium in biological samples by Urusova (1969).

The determination of titanium in excreta and human diets using arc-emission spectroscopy has been reported by Tipton & Stewart (1969) and Tipton et al. (1969). The limits of detection expressed as mg/kg ash were: food sample, 2; faeces, 9; and urine, 0.03.

Carroll et al. (1971) described the use of electron probe microanalysis for the determination of localized concentrations of titanium in various human tissues, both normal and pathological, as well as in human blood, bone marrow, leukocytes, and lymph nodes. The estimated detection limit was about 10^{-8} µg of metallic atoms per cell (Carroll & Tullis, 1968).

The concentration and distribution, in healthy human tissues, of a large number of stable elements including titanium was studied by Hamilton et al. (1972, 1973). The methods of analysis were spark-source mass spectroscopy and X-ray fluorescence. The detection limits for titanium in human tissues were 0.007 mg/kg for spark-source mass spectroscopy and 0.3 mg/kg wet weight for the XRF assay.

Alternating current polarographic determination of titanium in tissues has also been reported (Hoff & Jacobsen, 1971; Petit, 1973).

A histochemical method for the identification of titanium and iron oxides in pulmonary dust deposits was described by DeVries & Meijer (1968). The technique was especially developed for the study of pneumoconiosis in workers employed in industries processing these minerals. In this procedure, the oxides are converted, under heating, into water-soluble sulfates by fumes of sulfuric acid, after which the corresponding sulfates are identified by staining reactions.

3. SOURCES OF ENVIRONMENTAL POLLUTION

3.1 Natural Occurrence

Titanium is the ninth most abundant element in the earth's crust. It is widely distributed and occurs at an average concentration of 4400 mg/kg (Mason, 1966). It is usually found in the form of stable minerals, e.g., the end products of the weathering of basic rocks, principally ilmenite and rutile, and in the form of impurities or dispersions in many aluminosilicates (Vinogradov, 1959). Owing to its great affinity for oxygen and other elements, titanium does not exist in the metallic state in nature. A variable amount of titanium occurs in unweathered particles of clay, in amphibole, laepidomelane, and micas (Joffe & Pugh, 1934). The most common titanium minerals are ilmenite ($TiFeO_3$), which can contain a maximum concentration of titanium dioxide (TiO_2) of 530 g/kg, and rutile, which is 100% titanium dioxide. Titanium-bearing minerals such as anatase and brookite are associated with ilmenite and rutile. Other titanium minerals are known which are locally abundant in some deposits, but have not been used commercially. These include sphene ($CaTiSiO_5$), pyrophanite ($MnTiO_3$), and perovskite ($CaTiSiO_5$) (Stamper, 1970).

Both rock and sand deposits contain titanium minerals of economic importance. Some sand deposits containing less than 1% of titanium dioxide are commercially workable, if the principal titanium mineral is rutile. Titanium also occurs to a lesser degree in rocks such as brookite, anatase, and in feldspars, micas, biotites, and others in the form of isomorphic impurities. Rutile, ilmenite, brookite, and other common titanium minerals accumulate in sedimentary rocks and sometimes in certain soils as the end products of metamorphism of titanium-containing minerals and rocks. It is present in the form of titanium(IV) compounds; the rarer oxidation form of titanium(III) is also known in certain iron minerals as are complex titanium(IV) compounds (Vinogradov 1959; Stamper, 1970). Titanium levels in coal and oil have been reported to average 500 and 0.1 mg/kg, respectively (Bertine & Goldberg, 1971).

3.2 Industrial Production

Titanium is mined commercially from rock and sand deposits by open-pit and dredging operations. Mechanical beneficiation methods are used for concentrating the major minerals, ilmenite and rutile. The production of elemental titanium is a comparatively difficult process since titanium in the molten state has a great affinity for oxygen, nitrogen, and moisture in the air, as well as for carbon and most refractory materials. The principal method for the commercial production of titanium sponge metal is the Kroll process, which involves the reduction of titanium tetrachloride with magnesium metal in an inert atmosphere. Present commercial production by this method yields a titanium alloy of 99.5% purity that differs in hardness and strength from the pure titanium metal prepared from the thermal decomposition of titanium iodide (TiI_4). Titanium metal powder is usually produced by reaction of the metal with hydrogen; the resulting brittle titanium hydride is then crushed before heating in a vacuum to remove the hydrogen (Stamper, 1970).

Titanium dioxide of pigment quality is made by two distinct processes. In the sulfate process (Stamper, 1970; Katari et al., 1977), ground ilmenite or titanium slag is dissolved in sulfuric acid, reducing the iron present to the ferrous state. The titanium dioxide is then precipitated by hydrolysis together with part of the iron in the form of hydrated iron sulfates (copperas). The precipitated titanium dioxide is calcined at 900-1000 °C, treated by proprietary finishing processes, and ground to pigment size. In the chloride process (Katari et al., 1977), titanium tetrachloride is oxidized with air or oxygen and the resulting titanium dioxide calcined at approximately 500-600 °C to remove residual chlorine and any hydrogen chloride that may have formed in the reaction. Aluminium chloride is added to the titanium tetrachloride to assure that virtually all of the titanium is oxidized in the rutile crystalline form. After calcination, the titanium dioxide is treated by proprietary finishing processes as in the sulfate process.

There are about 30 commercially available grades of pure titanium and alloys. Elements in titanium alloys fall into two categories, i.e., those that strengthen and stabilize the alpha or room temperature modification, and those that strengthen the beta or high temperature modification. An alloy containing 6% aluminium and 4% vanadium comprises almost 50% of the total mill products used. Other alloys used widely include those containing either, 8% aluminium, 1% each of molybdenum, and vanadium, or 5% aluminium and 2.5% tin. Further aspects of the procedures dealing with the preparation and refining of titanium dioxide, titanium metal powder, and alloys have been dealt with in various monographs (Stamper, 1970; CEC, 1974; Katari et al., 1977).

The total world production of titanium concentrates in 1979 was 3.49 million tonnes of ilmenite (including leucoxene), 0.36 million tonnes of rutile, and 0.77 million tonnes of titaniferrous slag (Lynd & Hough, 1980). The approximate amount of titanium produced can be estimated knowing that rutile is 100% titanium dioxide and ilmenite has a theoretical maximum content of titanium dioxide of 53% (Stamper, 1970). Four countries together produced over 85% of the global production of ilmenite, i.e., Australia (33%),

Table 2. World production of titanium concentrates in 1979 (Values expressed in short tonnes = 907 kg)[a]

Country	Ilmenite and leucoxene	Rutile	Titaniferrous slag
Australia	1 280 646	305 773	
Brazil	20 000	400	
Canada			525 840
Finland	145 000		
India	165 000	10 000	
Japan			200
Malaysia	206 000		
Norway	903 576		
Portugal	200		
Sierra Leone[b]		11 000	
South Africa[b]		46 000	330 000
Sri Lanka	39 000	15 000	
USA	639 292	W[c]	
USSR[b]	450 000	10 000	
World total	3 848 714	398 173	856 040

[a] From: Lynd & Hough (1980).

[b] Estimated.

[c] W = witheld company proprietary data.

Norway (24%), USA (17%), and USSR (12%). Australia produced 77% of the total known world production (359 000 tonnes) of rutile. Practically all of the titaniferrous slag is produced by Canada (61.4%) and South Africa (38.5%) (Lynd & Hough, 1980). The world production figures for titanium concentrates are given in Table 2.

The recovery of titanium from secondary sources has so far been very modest, probably not exceeding 1% of the total production. However, it is likely to increase in the future. It has been calculated that the world demand for titanium in the year 2000 will range between 2.1 and 4.5 million tonnes. An estimate of ilmenite and rutile reserves is given in Table 3.

Table 3. Estimated world reserves of ilmenite and rutile[a]

Country	Million short tonnes[b]			
	Ilmenite	Titanium equivalent	Rutile	Titanium equivalent
Australia	20	5	4.0	2.0
Canada	100	25	0.5	0.250
India	60	15	0.1	0.050
Norway	120	30	-	-
Sierra Leone	-	-	3.0	1.50
Sri Lanka	5	1	0.3	0.150
United Arab Republic [Egypt]	40	10	-	-
USA	100	25	0.5	0.250
USSR	100	25	0.3	0.150
Other[c]	25	6	-	-

[a] From: Stamper (1970).
[b] US short tonne = 907 kg.
[c] Includes Brazil, China, Finland, Japan, Malaysia, Spain.

3.3 Uses of Titanium

Titanium, used as a construction material, is usually in the form of alloys, most of which have higher strength than pure titanium and enhanced corrosion resistance. About 95% of the titanium metal consumed in the USA is for aerospace applications, including aircraft and space craft. The remainder is used in the chemical and electrochemical processing industries, for handling some of the most corrosive processes, and in marine and ordnance applications.

Titanium is used in the paper pulp industry, because of its excellent resistance to organic acids, sulfides, and strong bleaches. It is also used in tubing, and in liners for vessels etc. in the production of nitric acid and acetaldehyde. The first large-scale industrial application of titanium was in the aluminium anodizing industry, where the metal supporting racks were made almost exclusively of titanium. Platinized titanium anodes are used in electroplating with gold, platinum, copper, silver, and other metals of high purity. Similar anodes are used in cathodic protection systems of ships, harbour installations, water heaters, and cleaning lines in the production of stainless steel strip. Another still expanding use of titanium metal is in surgical implant materials and prostheses.

Titanium dioxide (TiO_2) is by far the most important titanium compound. Because of its extreme whiteness and brightness, as well as its high index of refraction, titanium dioxide is extensively used as a white pigment primarily in surface coatings such as paints, lacquers, and enamels. It is estimated that over half of all non-permanent white or light-coloured surface coatings include a titanium dioxide level of 0.1-0.3 kg/litre. Over 17% of titanium dioxide is used in paper coatings or as paper fillers to improve opacity, brightness, and printability. The third largest and apparently fastest growing application of titanium dioxide is in the plastics industry, because of its resistance to degradation by ultraviolet light, high refractive index, whiteness, and chemical inertness (Stamper, 1970).

In addition, titanium dioxide is used in ceramic capacitors and electromechanical transducers, welding-rod coatings, and in the production of glass fibres. Miscellaneous applications of titanium dioxide pigment and other titanium compounds include the production of floor coverings, mainly of the synthetic resin types, rubber tyres, porcelain enamels, inks, wall coverings, artificial leather, oilcloth, upholstery materials, and other coated fabrics. Titanium dioxide is also used in the production of titanium carbides.

To a much lesser extent, titanium dioxide is used as a colour additive in the confectionery (Lorenz & Maga, 1973), food (Bone, 1967), and dairy industries (Kosikowski & Brown, 1969), as a potential additive for bread flours, replacing the normally used flour-bleaching agents (Lorenz & Maga, 1973), as a clouding agent for incorporation in dry beverage mixes (Carlson et al., 1972), and in tobacco wrapping (Detert & Buchholz, 1971).

Another commercially important compound is titanium tetrachloride ($TiCl_4$). It is primarily an intermediate in the production of titanium metal and pigments. It is also a component of Ziegler catalysts used for the low pressure polymerization of ethylene, propylene, and other hydrocarbons. Titanium tetrachloride is also widely employed as the intermediate raw material for the production of most organic titanium compounds, such as alkyl esters of titanium, alkyl titanates, other titanium esters, and butyl titanate (Feld & Cowe, 1965), which are used as cross-linking agents and catalysts.

Titanium trichloride ($TiCl_3$) is used for polymerization catalysts and as a colouring agent in molasses. It is prepared by reducing titanium tetrachloride. Some of the most common applications of titanium and its compounds are listed in Table 4.

Table 4. Some main applications of titanium and its compounds

Compounds	Use
titanium (Ti)	in alloys, aerospace, chemical processing industries
titanium dioxide (TiO_2)	pigments, paints, lacquers, printing, ceramics, as food additive, drug and cosmetic applications
titanium tetrachloride ($TiCl_4$)	polymerization (Ziegler type) catalyst, starting material for most organic compounds
titanium trichloride ($TiCl_3$)	polymerization catalyst
titanium carbide (TiC)	structural metals, alloys
organic titanium compounds	cross-linking agents, catalysts

3.4 Disposal of Wastes

The mining and concentration of titanium and the production of titanium dioxide generate large quantities of wastes. Disposal of these wastes and especially those generated by titanium pigment production is an important environmental problem for the industry. The waste also contains weak sulfuric acid. Large amounts of such processing wastes are dumped into the sea or river water (Peschiera & Freiherr, 1968; Elik, 1969; Fader, 1972; Weber, 1972; Häfele, 1974; Walsh, 1974; Katari et al., 1977). In the mining and beneficiation processes of ilmenite and in the production of titanium dioxide pigment, air pollutants are generated and sulfur dioxide and particulate matter containing titanium are emitted (Katari et al., 1977). Incineration of titanium-containing products such as paper, plastics, inks, and painted wood may contribute to the pollution of the air by titanium, which may subsequently enter the soil.

4. ENVIRONMENTAL LEVELS AND EXPOSURES

4.1 Levels in Air, Soil, Water, and Other Media

4.1.1 Air

Titanium concentrations in urban air are mainly below 0.1 µg/m³ and are still lower in rural air (Tabor & Warren, 1958; McMullen et al., 1970; US Environmental Protection Agency, 1973; Giauque et al., 1974). Concentrations exceeding 1.0 µg/m³ have occasionally been reported in urban air and especially in industrialized areas (Japan Environmental Sanitation Gentre, 1967; National Air Pollution Control Administration, 1969; Dams et al., 1970; US Environmental Protection Agency, 1973).

Tabor & Warren (1958), employing a semi-quantitative spectrographic method, studied the distribution of a number of metals including titanium in the atmosphere of several American cities. In 754 samples examined, detectable amounts of titanium (0.01 µg/m³) were not found in 23.3% of the samples, medium concentrations (0.01-0.1 µg/m³) were found in 71.4%, and high concentrations (0.1-0.3 µg/m³) in 5.3% of the samples. The combustion of coal and oil results in a discharge of trace amounts of several elements, including titanium, into the atmosphere. The principal sites of fossil fuel consumption are in the mid-latitudes of the Northern Hemisphere. Consequently, as was pointed out by Bertine & Goldberg (1971), the contribution to the titanium concentrations in air and natural waters will be most evident at these latitudes. Average concentrations of titanium of 500 mg/kg in coal and 0.1 mg/m³ in oil, have been reported.

Johansson (1974) determined the variation of titanium abundance with particle size in aerosols from North Florida, sampled near to the ground by a 5-stage cascade impactor in mainly unpolluted inland and coastal locations. The 32 separate size distributions were determined by proton-induced X-ray emission spectroscopy. Since titanium coheres with iron in most samples, and the ratios found were constant and close to the geochemical average of the ratios of these elements in soils, it was suggested that titanium had originated mainly from a soil source (yielding particles of 1 µm). For the smallest particles (0.25 µm), there was an indication of elevated titanium/iron ratios that might arise from an additional source of small particle titanium.

4.1.2 Soils and sediments

Though titanium is ubiquitous in its geographical distribution, regional levels vary considerably according to conditions such as weathering, fallout from consumption of fossil fuels, and incineration of refuse. Sandy soils, e.g., sand, bog, loess, and calcareous soils contain less titanium than heavy clay soils. According to an extensive review by Vinogradov (1959) of titanium values in soils from various parts of the world (e.g., Robinson, 1914; Tamm, 1925, 1930/1931); Agatomoff, 1928; Askew, 1930; Malac, 1931; Hirai & Buichiro, 1937; Ivanova & Koposov, 1937; Salminen, 1938; Lee, 1941; Monier-Williams, 1950), the average concentration in soil appears to be below 5 g/kg. However, some soils contain titanium dioxide at a concentration of about 10-100 g/kg.

Grabarov (1970) found that the titanium content of soils in Kazakhstan, USSR, ranged from 2 to 7 g/kg but that only 10-50 mg/kg was in a readily soluble form. Hussain & Islam (1971) measured titanium in soil, silt, and clay fractions of a number of soils from the Barind tract in Bangladesh. The mean titanium dioxide content in the soils ranged from 6 to 12 g/kg with an average value of 8 g/kg. The content in the clay fraction was higher than that in the silt fraction, with these soils showing signs of the development of argillic horizons.

Soils in the vicinity of power and incineration plants and industrial discharges may be enriched in heavy metals and trace elements. Klein & Russel (1973) reported that soils around a coal-burning power plant contained higher levels of trace metals than surrounding areas. The average level of titanium in soils in the vicinity of this power plant was 92 mg/kg compared with a background level of 56 mg/kg. The enriched area covered 300 km^2 with the enrichment confined to the upper 2 cm of soil.

4.1.3 Water

The concentration of titanium in water depends on both the amount of titanium dissolved in the water and on the quantity of titanium particles dispersed in the water. Titanium has been reported in all samples from 15 rivers in the USA and Canada in concentrations ranging from 2 to 107 µg/litre (Durum & Haffty, 1961). Durfor & Becker (1964) found titanium in 81% of 42 municipal water supplies in the USA at a mean concentration of 2.1 µg/litre with a range of 0.5-15 µg/litre.

Titanium levels in sea water have been reported to range from 1 to 9 µg/litre (Bowen, 1966; Mason, 1966). Titanium was found in 21% of the 24 samples collected along the entire coast of California, USA, the two highest concentrations being 0.7 µg/litre and 0.9 µg/litre (Silvey 1967). Ishibashi (1966) reported the distribution of 50 elements in sea water with levels of titanium averaging 0.65 µg/litre.

In studies by Hallsworth & Adams (1973), the heavy metal content of rainfall ash was compared with that of the fly ash from several power stations in the East Midlands of the United Kingdom. Levels of titanium in rainfall, which ranged from 6 to 7.8 g/kg of residues were roughly comparable with levels of titanium in the fly ash, which ranged from 3.6 to 7.5 g/kg.

4.1.4 Plants

Titanium, like aluminium, is found in relatively abundant quantities in the lithosphere and in soils, but is poorly absorbed and retained by plants (Underwood, 1977). Average titanium levels of approximately 1 mg/kg have been reported for a wide variety of plants (Bertrand & Voronca-Spirt, 1929a, 1929b). It has been suggested that levels in herbage samples are indicators of soil contamination (Barlow et al., 1960). Mitchell (1957) reported mean levels of titanium of 1.8 mg/kg (dry weight) in red clover (range 0.7-3.8 mg/kg) and 2.0 mg/kg in ryegrass (range 0.9-4.6 mg/kg) grown on different soils. In Kazakhstan, grain crops absorbed titanium levels of 50-100 g/ha and legumes 123-398 g/ha from soil containing levels of titanium of 1.2-7 mg/kg (Grabarov, 1970). More titanium was found in maple and elm leaves than in the leaves of other plants while the content of titanium in brush was 50-820 mg/kg.

4.1.5 Food

Large variations in the concentrations of titanium in different types of foods have been demonstrated. Schroeder et al. (1963) found whole grains, some vegetables and fruits, and common fish meat contained little or no detectable titanium (level of sensitivity = 0.025 mg/kg for tissues and 0.01 mg/kg for other materials) while higher levels ranging from 1.76 to 2.42 mg/kg wet weight were found in milled grains, butter, corn oil, corn-oil margarine, and lettuce. Wheat flour from the USA and Japan was found to contain 0.41 and 0.99 mg/kg (wet weight), respectively; corn oil and corn-oil margarine levels were 0.83 and 1.80 mg/kg (wet weight), respectively. In a study by Asmaeva & Il'vickij (1969), levels of titanium in grains were related to the region of growth and climatic conditions.

Though titanium is poorly absorbed and retained by both animals and plants (Monier-Williams, 1950; Underwood, 1977), higher concentrations of titanium can potentially occur in food crops in localized areas as a result of soil contamination by: fly ash fallout (Hallsworth & Adams, 1973; Klein & Russel, 1973; Capes et al., 1974); industrial contamination (Tarabrin, 1970); and use of industrial, household, and sewage residues for the fertilization of vegetable plots (Leščenko et al., 1972). Some algae are able to accumulate titanium up to 10 000 times and possess the potential to introduce large quantities into the food chain (Schroeder et al., 1963).

High concentrations of titanium in food, especially cheese, can arise from the use of titanium dioxide as a whitener in the manufacture of mozzarella cheese (Kosikowski & Brown, 1969; Leone, 1973). Titanium is also used in the production of niva and Edam cheese to accelerate aging and improve quality (Palo, 1966, 1967).

4.2 Occupational Exposure

Nearly all exposures to titanium are to dusts, though some exposure to fume and vapour occurs in handling titanium tetrachloride. Occupational exposure to titanium mainly occurs in the mining and production of the metal, and in the production and processing of titanium dioxide and carbide. During the extraction and recovery of titanium from its major ores such as ilmenite and rutile, the atmospheric concentrations of the ores may reach levels commonly regarded as the maximum permissible for inert or nuisance dusts. In the preparation of raw materials, i.e., crushing, grinding, mixing, and sieving of rutile concentrates and technical grade titanium dioxide - the concentration of dust depends on the humidity of the air and on the materials treated. According to Kokorev et al. (1960), the dust concentration in the air of crushing rooms, containers, and transporters, amounted to 4-6 mg/m^3. Considerable concentrations of titanium tetrachloride vapour were found in the chlorine department. In some other departments, such as the crushing and classification departments, the concentration of titanium dust (titanium-rich slag containing about 70% titanium dioxide) may reach 30-50 mg/m^3.

Exposure to titanium and its compounds occurs not only in the production of metallic titanium, but also in processes in which it is used. According to Mezenceva et al. (1963), in the production of hard alloys, the dust concentration in the air during the sieving of titanium carbide ranged from 20.3 to 40.2 mg/m^3, while in the process of carbonization, it amounted to 22 mg/m^3.

Škurko & Brahnova (1973) reported high concentrations of titanium dust in the breathing zone of workers employed in the manufacture of titanium hydride. High mean concentrations up to 500 mg/m^3 were found in the hydrogenation shop, manual handling, screening, and packaging of the powder. Cleaning of the retort resulted in a mean concentration of 210 mg/m^3.

4.3 Cosmetic and Medical Uses

A variety of drug and cosmetic applications for titanium dioxide exist based primarily on its effectiveness: as a short-wave ultraviolet sunscreen (Vickers, 1967; MacLeod & Frain-Bell, 1971); in the treatment of herpes simplex (Scott, 1969; Shuster 1971) and photosensitive cheilitis (Rich et al., 1971); in dermatological and cosmetic formulations (Rudowską, 1967; Miller & Gilmore, 1971); as an anti-acne ointment (Fuga, 1967) and an anti-inflammatory ointment for gums and oral mucosas (Lakovska et al., 1971); in removal, by tattooing, of facial haemangiomas (Hage, 1967); and in a variety of tablet-coating formulations (Lindberg & Jonsson, 1972; Hortobagyi, 1973).

Mention should be made of the increasing use of titanium in metal plates, pins, nuts, and bolts in contact with various tissues (Beder & Eade, 1956; Beder et al., 1957).

4.4 Estimate of Exposure of Man through Environmental Media

Food is the principal source of exposure to titanium for man. This is obvious from the concentrations of titanium in food, water, and air (sections 4.1.1-4.1.5). As titanium has not been proved to be an essential element for man and is not very noxious, only a few dietary intake and balance studies have been undertaken. Recent studies are not available and the results from earlier studies are not always very representative.

Because of the variations in diet, as well as the variations in total food consumption in different parts of the world (Hamilton & Minski, 1972/1973), it is very difficult to estimate the daily intake of titanium. Typical American diets were estimated by Schroeder et al. (1963) to provide approximately 300 μg of titanium daily. Tipton et al. (1966) reported the 30-day mean total American dietary titanium intakes of two individuals to be 370 and 410 μg/day. The daily titanium intake for two men (23 and 25 years old), over a period of 50 weeks, was reported by Tipton et al. (1969) to be 750 ± 80 μg and 2000 ± 400 μg, respectively. The dietary content of titanium was measured from estimated (i.e., not weighed) duplicates of every ingested item. Hamilton & Minski (1972/1973) reported a daily intake of about 800 μg from the United Kingdom and ICRP (1959) arrived at an estimate of 540 μg. The daily intake of titanium from drinking-water is usually very low, probably below 5 μg/day.

Outside occupational settings, the amount of titanium absorbed via the lungs is of little significance in relation to the intake from food, and the intake by inhalation is less than 1% of the total intake. Assuming a respiratory volume of 15 m^3/day, the intake would vary from almost none to 4.5 μg with an average of about 0.75 μg, but it can be expected that only one-third or less of the inspired titanium is retained in the lungs (Schroeder et al., 1963). Woolrich (1973), basing his estimates on surveys in four American cities, calculated the daily intake from air to be approximately 3.8 μg of titanium assuming that 20 m^3 air per day is respired, with a maximum concentration of 0.19 μg/m^3.

In the working environment, where the air concentration may reach several mg/m^3, exposure through inhalation is of greater importance. Data on pulmonary retention as well as absorption of swallowed particles are insufficient to make any estimate of the exposure in various occupational environments. However, several autopsy studies on workers occupationally exposed to titanium dioxide dust have shown the presence of titanium in the lungs in concentrations clearly exceeding those found in the lungs of unexposed subjects (Schmitz-Moorman et al., 1964; Elo et al., 1972; Ophus et al., 1979).

5. CHEMOBIOKINETICS AND METABOLISM

5.1 Absorption, Distribution, and Excretion

5.1.1 Animal studies

Data on the absorption of titanium compounds are very limited and very little quantitative information is available with regard to absorption by inhalation. Ingested titanium is apparently absorbed from the gastrointestinal tract (Schroeder et al., 1964) but there is little information regarding the extent of absorption, and comparative studies using different titanium compounds have not been made. Lloyd et al. (1955) tested the suitability of titanium dioxide as a marker for digestibility. The recovery of only 92% of the titanium dioxide fed to rats at a dietary level of 2.5 g/kg remained largely unexplained. The minute absorption of titanium from the gastrointestinal tract was demonstrated in a study in which mice were given ^{44}Ti intragastrically (without marker). The whole body count after 24 h did not exceed the background level (Thomas & Archuleta, 1980). A comparison of organ contents of ^{44}Ti after oral and intravenous administration of the isotope (3 µCi), indicated a gastrointestinal absorption of less than 5% in lambs (Miller et al., 1976). When male and female rats were fed a diet containing titanium dioxide (100 g/kg) for a period of about 32 days, a significant retention of titanium of 0.06 and 0.11 mg/kg wet weight was found only in the muscles; no retention was observed in the liver, spleen, kidney, bone, plasma, or erythrocytes (West & Wyzan, 1963). The same authors administered 5 g of titanium dioxide to 5 male adult volunteers on 3 consecutive days. This did not cause any significant increase in the urinary content of titanium.

The clearance of titanium dioxide from the lungs was studied in rats after inhalation of 15 or 100 mg/m^3. The average median aerodynamic diameter of the titanium dioxide particles was 1.48 µm. After a single exposure, about 40-45% of the deposited particles were cleared from the lung in 25 days. At 15 mg/m^3, 0.7% was found in the hilar lymph nodes indicating penetration of titanium dioxide particles from alveoli into the lymphatic system and partial clearance by the lymphatic route. The clearance rate was similar after intratracheal administration of titanium dioxide. At an exposure of 100 mg/m^3, the clearance rate decreased drastically (Ferin & Feldstein, 1978). Elo et al. (1972) demonstrated the presence of titanium dioxide in the lymphatic systems of 3 workers employed in processing titanium dioxide pigments.

The distribution of titanium in the organs of mice following the administration of a tetravalent, soluble titanium salt (titanium potassium oxalate) in drinking-water at a concentration of 5 mg/litre was reported from a life span study by Schroeder et al. (1964). The results were compared with organ concentrations in control mice fed drinking-water without the addition of titanium, and in wild field mice (Table 5). Organs of treated and wild animals displayed concentrations of roughly the same order of magnitude, whereas untreated mice showed lower levels, the differences being more pronounced in males.

Table 5. Titanium concentrations in the organs of mice given titanium in the drinking-water at 5 mg/litre throughout the life span (values in mg/kg wet weight)[a]

	No.	Heart	Lung	Spleen	Liver	Kidney
Treated mice						
Male	41	8.80	4.81	6.83	1.81	2.86
Female	37	4.10	1.66	3.70	2.05	2.89
Untreated mice						
Male	31	0.34	0.13	0.94	0.38	0.33
Female	51	1.08	0.66	1.10	0.67	0.55
Wild field mice	9	6.93	3.03	-	4.10	1.03

[a] From: Schroeder et al. (1964).

Following intravenous injection of rats with 50 mg of titanium dioxide (250 mg/kg body weight), there was an exponential disappearance rate with only about 30% remaining after 10 min. After intravenous injection of 250 mg/kg body weight of titanium dioxide in rats, about 70% of the injected dose was detected in the liver, 5 min after administration, and almost 80%, 15 min after injection. The highest concentration was found in the liver followed by the spleen after 6 h, whereas, after 24 h, the highest concentration was found in the celiac lymph nodes, which filter the lymph from the liver. One year after the injection, the highest concentrations were still found in these lymph nodes (Huggins & Froehlich, 1966).

5.1.2 Human studies

Little information is available on the absorption of titanium compounds by man. With respect to absorption by inhalation, there is evidence showing that titanium containing particles in the air are in the upper respirable size range (Johansson, 1974). The titanium retained in the peripheral part of the lungs does not seem to account for the observed titanium levels in lung tissue (Schroeder et al., 1963). Experiments on rats suggest that titanium may be taken up by the lungs from the blood. On the basis of rather rough calculations, Schroeder et al. (1963) concluded that a third or less of the inspired titanium may be retained in the lungs.

Few studies have been reported on the absorption of titanium from the gastrointestinal tract in man. Perry & Perry (1959) reported a mean concentration of 10 μg/litre in pooled urine indicating absorption; however, the extent of the absorption is not known. Accepting this amount in the urine, and assuming a daily intake of 300 μg of titanium, Schroeder et al. (1963) calculated that about 3% of the dietary dose would be absorbed.

Wide variations in titanium levels in different organs in man have been found, the lungs frequently containing the highest amount. Hamilton et al. (1972/1973) using X-ray fluorescence found concentrations of 3.7 mg/kg wet weight in the lung and 0.8 mg/kg in the brain, demonstrating that titanium passes the blood-brain barrier. Earlier, Tipton & Cook (1963) and Schroeder et al. (1963) had also found that concentrations in lung tissue were higher than in other human tissues. In a male worker not occupationally exposed to metals, the highest concentration was found in the hilar lymph nodes (150 mg/kg dry weight) followed by the lung (33 mg/kg dry weight) (Teraoka, 1980). Comparison of tissue levels of titanium between American subjects and people from other geographical areas showed similar high concentrations in pulmonary tissues (Perry et al., 1962).

In the study by Schroeder et al. (1963), accumulation of titanium started in the lung after the third decade and did not occur in the kidney, skin, or aorta. Infant kidneys contained several times the adult concentration of titanium (Tipton & Cook, 1963).

Metal and mineral concentrations in the lungs of West Virginian bituminous coal miners were studied by Crable et al. (1967, 1968). The mean concentration of titanium, among other metallic constituents, in the lungs of 26 miners (with 23-50 years service) was 119 mg/kg dry weight compared with a normal level of 19 mg/kg. Röthig & Wehran (1972) found concentrations of titanium in the lungs of patients with silicosis ranging from 4 to 24.3 mg/kg. Levels in the lymph nodes ranged from 12.2 to 120 mg/kg. The average titanium concentration rose with increasing severity of silicosis, the concentration of titanium in the hilar lymph nodes being much higher than that found in the lungs.

A mean titanium concentration in blood of 0.07 mg/litre was reported by Hamilton et al. (1972/1973), not much different from the 0.02-0.03 mg/litre previously reported by Maillard & Ettori (1936a; 1936b). A somewhat higher mean level of 0.123±0.005 mg/litre was found in 20 healthy subjects, 20-43 years of age, by Možajceva (1970). Timakin et al. (1967) reported a mean level of 0.054±0.002 mg/litre in the serum of 200 healthy persons from the USSR. Smyšljaeva et al. (1971) determined the distribution of titanium in the blood of children in the age range of 1-14 years. They found a ratio of 2:3 between erythrocytes and plasma; this ratio decreased slightly with age. The range of the ratios was 0.5-1.

Titanium was qualitatively detected in leukocytes, using electron probe microanalysis (Carroll & Tullis, 1968). There are some indications that titanium levels in the blood may change in a variety of diseased states (Bredihin & Soroka, 1969; Kas'janenko & Kul'skaja, 1969; Možajceva, 1970; Alhimov et al., 1971).

Schroeder et al. (1963) demonstrated the presence of titanium in the tissues of newborn infants, indicating that titanium passes the placenta. The fact that titanium was not detectable in all fetuses may reflect the sensitivity of the analytical methods used; however, Scanlon (1975) interpreted this finding as evidence of titanium not being an essential element for man.

Most of ingested titanium is eliminated unabsorbed with the faeces. Under normal circumstances, titanium is excreted with the urine probably at a rate of about 10 µg/litre (Perry & Perry, 1959; Schroeder et al., 1963). Higher urinary excretion levels of 0.41 and 0.46 mg/litre have been reported in two adults (Tipton et al., 1966). Other routes of excretion are not known.

5.1.3 Biological half-life

Few attempts have been made to calculate the biological half-life of titanium in man or experimental animals. The lung is considered to be the primary target organ in man and the residence time of titanium dioxide in the lung has been regarded as long (ICRP, 1959). In one report, the biological half-life of titanium in man was calculated to be 320 days (ICRP, 1959). Following the intraperitoneal and intravenous administration of ^{44}Ti in mice, a mean biological half-life of 640 days was calculated. On the basis of experience with the biological half-life of uranium dioxide in rats, monkeys, and dogs, the authors speculated that the whole-body retention of titanium in man may be even longer than the reported 640 days in mice (Thomas & Archuleta, 1980).

6. EFFECTS ON ANIMALS

6.1 Acute Toxicity

When administered to rats as a single intraperitoneal injection of 25 mg (139-156 mg/kg body weight) (Sethi et al., 1973) or an intravenous injection of 250 mg/kg body weight (Huggins & Froehlich, 1966), titanium dioxide behaved as an inert substance.

Studies on titanates suspended in corn oil revealed that the intraperitoneal LD_{50} for rats was 3.0 g/kg body weight for barium titanate, 2.2 g/kg body weight for bismuth titanate, 5.3 g/kg for calcium titanate, and 2.0 g/kg for lead titanate. The corresponding oral LD_{50} was more than 12 g/kg body weight (Brown & Mastromatteo, 1962).

Titanium dioxide (TiO_2) has been used as inert dust particles in lung clearance studies on animals (Ferin 1971a, 1971b, 1972; Ferin & Leach, 1973). Observations made 2 months after intratracheal injection of titanium dioxide (20 mg/animal) in rats did not reveal any reactions other than non-specific responses to dust particles (Göthe & Swensson, 1970).

Short-term exposure of guinea-pigs to titanium dioxide aerosol did not induce any inflammatory response; the number of leukocytes and macrophages remained normal, whereas dusts with a toxic potential, such as the dioxides of silicon (SiO_2) and manganese (MnO_2) caused an increase in the number of leukocytes (Rylander et al., 1979). The biological inertness of titanium dioxide was further demonstrated in that it did not exert any demonstrable effect on the viability of alveolar macrophages (Määttä & Arstila, 1975); moreover, titanium dioxide did not cause fibroblasts to produce hydroxyproline indicating a lack of fibrogenicity (Heppleston, 1971). When the synthesis of collagen increases, the level of proline hydroxylase (EC 1.14.11.2) in lung tissue increases. This was shown to occur in rats a few weeks after exposure to silica (Halme et al., 1970). In a study by Zitting & Skyttä (1979), a suspension containing 50 mg of titanium dioxide dust in 0.5 ml saline was administered to rats by pipetting into the pharynx. This did not result in increased levels of proline hydroxylase. In vitro haemolysis of erythrocytes has been suggested as a model for the biological activity of dusts (Macnab & Harrington, 1967). It was, however, noted that while rutile pigments did not have any haemolytic effect in vitro, the anatase pigments as well as a mixture of anatase and rutile did exhibit such an effect (Zitting & Skyttä, 1979). The reasons for differences in the effects of rutile and anatase dusts could not be explained, but the report points to the importance of studying titanium dioxide pigments in relation to their type of crystal lattice.

Inhalation of titanium tetrachloride (aerosols of its hydrolitic products, i.e., titanium compounds and hydrogen chloride) caused a higher death rate and more rapid development of lung oedema in mice than inhalation of an equivalent concentration of hydrogen chloride (Mel'nikova, 1958; Mezenceva et al., 1963; Mogilevskaja, 1973). This higher toxicity appears to be associated with the adsorption of hydrogen chloride on particles of hydrated titanium oxide which penetrate to the deeper parts of the lung not usually reached by the highly soluble hydrogen chloride. Particles containing intermediate products of titanium tetrachloride hydrolysis are deposited in the alveoli, where hydrolysis continues causing additional damage to the lung tissue.

Similar effects were observed in mice and rats by Sanockij (1961). Titanium tetrachloride also caused purulent conjunctivitis and corneal opacity in rabbit eyes.

6.2 Subacute Toxicity

The general inertness of titanium metal has been demonstrated in various implantation studies. Beder & Eade (1956) studied the effects of discs of titanium metal implanted in the muscle tissue of dogs and left in situ for 7 months. The tolerance of soft tissue and bone to contact with titanium was illustrated by lack of irritation, normality of wound-healing and the encapsulation of the metal by fibrous tissue. Similar inertness and lack of response in the bone tissue of dogs was reported by Beder et al. (1957), 120-180 days after the plating and fixation of fractures using titanium plates.

Studies on the intratracheal injection of 400 mg of titanium dioxide in rabbits and observation after 3 months did not reveal any reactions other than non-specific responses to dust particles, such as an increase in numbers of phagocytes (Dale, 1973). Intratracheal instillation of a total dose of 75 mg of barium tetratitanate suspended in saline (50 g/litre), given in 3 weekly doses to guinea-pigs did not induce any signs of fibrotic reaction, up to 12 months after administration (Pratt et al., 1953). Similar results were achieved by Wozniak et al. (1976), who gave rats 50 mg of titanium dioxide intratracheally. No fibrosis was found in the lungs after 3 months.

A fibrotic effect on eosinophilic infiltration was noted in guinea-pigs (Lenzi, 1936) following repeated titanium dioxide inhalation over various time intervals ranging from 5 days to 4 months. The dose administered was not reported but

A single intratracheal injection of a suspension of 50 mg of metallic titanium dust or titanium dioxide dust was administered to 5-7 rats. Sacrifice of some animals after 6 months and sacrifice of the remaining animals, which had been injected a second time, after 11 months did not reveal any nodular processes or interstitial sclerosis. Minor effects on the lungs after the second injection were limited to some lympho-histiocytic reaction around the particles (Mogilevskaja, 1956). In another study, Mogilevskaja (1961) administered 50 mg of a titanium concentrate (ilmenite) intratracheally to 8 rats and sacrificed the animals after 5 and 7 months. She found slight fibrogenic activity in the lungs. The ilmenite contained silica (SiO_2) at 15-20 g/kg, aluminium(III)oxide (Al_2O_3) at 5-35 g/kg, iron(II)oxide (FeO) at 270-320 g/kg, and iron(III)oxide (Fe_2O_3) at 170-230 g/kg.

Schlipköter et al. (1971) administered 48 mg of titanium dioxide and 2 mg of quartz (particle size, 5 µm) intratracheally to 60 rats. Thirty of the rats were injected subcutaneously every 8 weeks with 2 ml of a solution of polyvinylpyridine-N-oxide (PVNO) (20 g/litre). When sacrificed after 12 months, the animals treated with only the titanium-silica dust showed advanced fibrosis, whereas the PVNO-treated rats were found to have an inert deposition of dust in the lungs and lymph nodes without any sign of fibrosis. The hydroxyproline content of the lungs in PVNO-treated animals did not differ significantly from that in rats treated with only titanium dioxide but was lower than that in rats given titanium-silica dust. As PVNO inhibits silica (SiO_2) specifically, the fibrogenic activity was likely to be due to the quartz added to the titanium dioxide.

Inhalation studies using needle-like potassium octatitanate fibres (average length 6.7 µm, diameter 0.2 µm) in doses ranging from 2.9 to 41.8 x 10^6 fibres (5 µm in length) per litre for 3 months (6 h daily) induced a dose-related fibrosis in rats, hamsters, and guinea-pigs, 15-24 months later (Lee et al., 1981). A dose-related fibrosis was also noted in rats receiving titanium phosphate fibres (length 10-20 µm, diameter 0.2-0.3 µm) intratracheally. The titanium phosphate fibre is a man-made fibre that has a potential use for replacing asbestos in various applications (Gross et al., 1977).

Intratracheal administration of 50 mg of titanium nitride (TiN) to rats was reported to induce a weak fibrogenic effect after 6 months (Brahnova & Samsonov, 1970). The oxyproline content of the lungs of rats exposed to titanium hydride (TiH_2) dust was increased, but the increase was only about 16-20% of that induced by silica. These effects were accompanied by dystrophic changes in the myocardium, liver, and kidneys (Škurko & Brahnova, 1973) as well as biochemical changes that, according to the authors, indicated abnormalities in protein metabolism (Brahnova & Škurko, 1973). Brahnova (1969) compared the effects on animals of different dusts containing transition metal borides or carbides, including those of titanium, over a 1-12 month period with respect to their electron structure. An elevated fibrogenic action and pronounced dystrophy of the liver, kidneys, and sometimes of the myocardium were found to occur to a greater extent with the borides than with the carbides.

A group of 10 male and 10 female rats was given N.F. grade titanium dioxide in the diet at 100 g/kg, for 30-34 days. A second group did not receive the titanium dioxide. All animals remained healthy and behaved normally. Weight gain and food intake were comparable for the 2 groups. No relevant gross pathology was observed at autopsy (West & Wyzan, 1963).

Three groups of 2 dogs each, were respectively given 0.05, 0.1, and 0.15 g of titanium dioxide, orally. Every 5 days, the dose was increased by the original amount. One dog out of each group was kept for 1 month, the other, for 2 months. No toxic effects were seen with regard to haematology, gross pathology, and histopathology. Three dogs received weekly subcutaneous injections of a suspension of titanium dioxide in oil; the initial dose of 500 mg was raised progressively to 3 g over 7 weeks. The 3 dogs survived without adverse effects. A fourth dog, which initially received 250 mg/kg rising to 2 g/kg body weight, died, but death, according to the author, was not causally connected with the administration of titanium dioxide (Vernetti-Blina, 1928).

6.3 Long-term Toxicity

Schroeder et al. (1964) administered titanium potassium oxalate, at a concentration of 5 mg/litre, in the drinking-water of Swiss Charles River mice, from weaning to natural death. The control group consisted of 88 female and 61 male mice compared with 53 female and 54 male mice in the treated group. The survival rate after 18 months was 75% females and 50% males for the control animals, and 70% females and 40% males for the treated group. The body weights of the animals in the titanium-fed group were higher than those in the control group.

Two guinea-pigs, 2 rabbits, 2 cats, and 1 dog were fed technical grade titanium dioxide for 390 days. The dog received 9 g/day, the rabbits and cats, 3 g/day, and the guinea-pigs, 0.6 g/day. Two additional cats received 3 g titanium dioxide daily for 175 and 300 days, respectively. Adverse effects were not seen in any of the animals and histopathological examination did not reveal any abnormalities (Lehman & Herget, 1927).

Christie et al. (1963) did not find any evidence of pathological response in the lungs of rats that had inhaled titanium dioxide dust (air concentrations in the range of 10-328 million particles per cubic foot) 4 times daily, 5 days per week for periods up to 13 months, followed by a 7-month period of fresh air. The inhalation of titanium dioxide did not affect the weight of the rats.

6.4 Mutagenicity

Evidence of mutagenic activity of titanium or its compounds is scant. Levan (1945) described cytological reactions induced in the stems of *Allium cepa* by a large variety of inorganic salt solutions. Titanium salts induced sticky chromosomes manifested by the formation of anaphase bridges. Titanium tetrachloride has been claimed to be non-mutagenic (Hsie et al., 1979). Some titanium compounds have been tested using the "rec-assay" with *Bacillus subtilis*. The following compounds were found to be negative in the "rec-assay": titanium tetrachloride ($TiCl_4$), titanium trichloride ($TiCl_3$), titanium boride (TiB_2), titanium carbide (TiC), titanium fluoride (TiF_4), and titanium dioxide (TiO_2) (Kada et al., 1980).

6.5 Carcinogenicity

Few studies have been carried out on the carcinogenicity of titanium and its compounds.

Furst (1971) reported that titanium metal (pure powder of at least 200 mesh) injected intramuscularly in 6 monthly doses, each of 6 mg in 0.2 ml trioctanoin, induced 2 fibrosarcomas in 25 male and 25 female Fisher-344 inbred rats and lymphosarcomas in 3 out of 25 males. Fibrosarcomas or lymphomas were not seen in the controls given trioctanoin alone. Treated rats survived up to 820 days and controls up to 935 days.

When a suspension of lead titanate in saline (10 g/litre) was administered intratracheally to 6 guinea-pigs (0.3 ml, once every 3 months) for a total of 6 injections, it did not give rise to tumours (Steffee & Baetjer, 1965).

In the longevity study by Schroeder et al. (1964), described in section 6.3, the mice receiving titanium throughout their life-time did not show any increase in the tumour incidence compared with the control mice.

Titanocene, a laboratory experimental compound, was shown to be carcinogenic, when suspended in trioctanoin and injected intramuscularly into Fischer-344 rats, once a month, to give a total administered dose of 200 mg. Fibrosarcomas developed in the thigh muscle at the site of injection. In addition, some of the treated animals developed hepatomas and malignant lymphomas of the spleen. The control compound, titanium dioxide was reported to have induced only 3 fibrosarcomas in 3 out of 50 rats. Details of the study were not reported (Furst & Haro, 1969).

It has recently been shown that metallocene dichlorides, $(C_5H_5)_2MCl_2$, where M = titanium, vanadium, molybdenum, or nobium, exhibit cancerostatic activity against the Ehrlich ascites tumour system in mice, and that treatment with such metals has lead to total cures. According to Köpf-Maier & Köpf (1980), the mechanism behind the cancerostatic effect of titanocene dichloride is not known. The antitumor activity has been investigated in mice, using single intraperitoneal injections of titanocene dihalides at doses ranging from 10 to 240 mg/kg body weight. Survival times without manifestations of tumours, were significantly longer in treated, than in control animals (Köpf-Maier et al., 1980a, 1980b; Köpf-Maier & Krahl, 1981).

On the basis of available data, titanium has generally been considered to belong to the group of metals of low carcinogenicity (Sunderman, 1978; Radding & Furst, 1980; Valentin & Schaller, 1980).

6.6 Teratogenicity and Effects on Reproduction

Schroeder & Mitchener (1971) studied the toxic effects of titanium on the reproduction of mice and rats. Breeding mice of the Charles Rivers CD strain and rats of the Long-Evans BLUE: (LE) strain were exposed in separate studies to titanium in the form of a soluble salt in the drinking-water (concentration 5 mg Ti/litre). Each group was carried through 3 generations. The data on rats are summarized in Table 6.

In rats, the titanium was toxic with a marked reduction in the numbers of animals surviving to the third generation, only 2 litters appearing in this generation. The male/female ratio was progressively reduced. The controls continued to breed for 4 generations with few deaths and runts occurring.

Table 6. Results of a 3-generation study on rats receiving titanium in the drinking-water[a]

	Number litters	Average litters	M/F ratio	Maternal deaths	Dead litters	Young deaths	Runts	No. rats
F_1 generation								
control	10	11.4	1.14	0	0	0	0	114
titanium	11	9.4	1.43	0	0	1	23	103
F_2 generation								
control	10	11.3	1.10	0	0	0	1	113
titanium	16	10.9	0.99	1	0	24	14	174
F_3 generation								
control	11	11.0	1.06	0	0	1	0	121
titanium	2	8.0	0.60	0	0	0	6	16

[a] From: Schroeder & Mitchener (1971).

7. EFFECTS ON MAN - CLINICAL AND EPIDEMIOLOGICAL STUDIES

7.1 Clinical Studies

Elo et al. (1972) examined lung specimens from 3 factory workers employed for 9 years in processing titanium dioxide pigments. Significantly higher titanium levels were found in the lungs of these patients compared with lung specimens from a general autopsy population. Deposits in pulmonary interstitium were associated with cell destruction and slight fibrosis. Titanium dioxide was found in the lymphatic system, suggesting that it was cleared via this route. Electron-microscopic studies revealed titanium dioxide particles within lysosomes of the alveolar macrophages. It was suggested that industrially processed titanium dioxide, either alone or in conjunction with other compounds such as silica, may behave as a mild pulmonary irritant. Using X-ray microanalytical light and electron-microscopic methods, open lung biopsy samples and sputum specimens from 3 former workers exposed to titanium dioxide were studied by the same investigators. These studies revealed that, in addition to titanium, the alveolar macrophages contained small amounts of silicon, aluminium, iron, and potassium. As industrial titanium dioxide is mostly coated with various other elements such as aluminum and silicon, and because these substances were localized in different structures of the lung, it was postulated that the weak fibrogenic effect was exerted by silica or silicon compounds rather than by the titanium dioxide (Määttä & Arstila, 1975).

Autopsy studies on workers exposed to titanium dust have generally corroborated experimental animal studies showing that titanium dioxide dust does not exert any fibrogenic effect on lung tissues. Extensive titanium dioxide deposits were found in the lungs of a worker who had been exposed to titanium dioxide dust for 15 years. However, no inflammatory or fibrotic changes could be seen (Schmitz-Moorman et al., 1964). In a more recent autopsy study on a 55-year old man who had been exposed to titanium dioxide, the crystal modification was taken into consideration. The methods used included scanning and transmission electron microscopy, electron X-ray diffractometry, and atomic absorption spectroscopy. Considerable deposits of rutile were found, but there were not any signs of fibrotic changes (Ophus et al., 1979). Husten (1959) reported fibrosis in a worker who had been exposed in the hard metal industry. The study is quoted as an indication of a possible fibrogenic effect of titanium (American Conference of Governmental Industrial Hygienists, 1973). However, this worker had been exposed to other elements more likely to be responsible for the fibrosis, a feature occasionally seen in workers in the hard metal industry (Parkes, 1974; Konietzko et al., 1980).

Accidental exposure to titanium tetrachloride ($TiCl_4$) fumes was described by Heimendinger & Klotz (1956). Splashing with titanium tetrachloride at 100 °C and inhalation of fumes of titanic acid and titanic oxychloride led to surface skin burns with scarring. The mucosa of the pharynx, vocal cords, and trachea was markedly congested with cicatrization and laryngeal stenosis as late sequelae. Histology showed titanium dioxide phagocytosed in the lungs. Larger dust deposits were associated with small areas of focal emphysema, but no specific lesion was seen. Lawson (1961) reported 3 cases of accidental exposure to titanium tetrachloride liquid, which was then washed off. Contact with water resulted in severe burns due to the exothermic reaction between titanium tetrachloride and water. Later sequelae were pigmentation and scarring. Nine other mild cases showed less severe burns, without subsequent permanent skin changes. However, contact with a 10% solution of titanium tetrachloride can cause second and third degree burns in man (Mogilevskaja, 1973), and precautions have to be taken in handling titanium tetrachloride to protect occupationally-exposed workers (Kokorev et al., 1960; American Conference of Governmental Industrial Hygienists, 1973).

The lack of toxicity of titanium and its compounds in contact with the skin has been demonstrated by its use in the therapy of skin disorders. Titanium compounds (salicylate, peroxide, oxides, tannate) have been used for many skin disorders (Ereaux, 1955). During the Second World War, a protective film of cream containing titanium dioxide was used on exposed parts of the body to prevent flash burns (Fairhall, 1969). Déribéré (1941) has described its innocuous use as a constituent of cosmetic preparations.

Titanium is accepted as a biocompatible implant material in orthopaedics, oral surgery, and neurosurgery. It has extremely high corrosion resistance and does not cause adverse tissue reaction (Williams & Adams, 1976; Palmer et al., 1979; Solar et al., 1979; Schroeder et al., 1981). Small amounts of titanium may occasionally be found in tissues adjacent to the implant (Laing et al., 1967; Meachim & Williams, 1973). The mechanism of the release of titanium is not well understood as it seems to be unrelated to wear processes (Williams & Adams, 1976; Solar et al., 1979). No harmful effects have been reported to follow such a release of titanium from implants. Harmful immunological reactions to titanium have not been demonstrated (Lyell, 1979; Brun & Hunziker, 1980).

7.2 Epidemiological Studies

Epidemiological surveys have focused, almost exclusively, on the possible fibrogenicity of titanium dioxide dusts. An early study conducted by Vernetti-Blina (1928) on men exposed to titanium dust for prolonged periods did not reveal any sign of abnormality in the clinical, radiological, or blood picture. Uragoda & Pinto (1972) investigated the health of 136 workers in an ilmenite extracting plant, in Sri Lanka. The workers were exposed to a number of minerals, the principal ores of which were ilmenite, rutile, and zircon. The prevalence of changes in the chest radiographs did not differ between the workers and a reference group drawn from the general population. Furthermore, Moschinski et al. (1959) did not detect any fibrosis in titanium dioxide-exposed workers.

Daum et al. (1977) studied 207 workers exposed to titanium dioxide in a plant producing the dioxide from ilmenite ore using the sulfate process. Ninety per cent of the workers had been exposed for 20 years or more. Spirometry revealed obstruction of the airways in 47%, but pneumoconiotic changes in the chest radiographs were "relatively few and unrelated to the respiratory abnormalities observed". It was pointed out by the authors, and by Parkes (1977), that the sulfate process may cause irritation of the upper respiratory tract, and that this probably caused the abnormalities found in the study, rather than the titanium dioxide dust.

In a survey of workers in factories manufacturing titanium tetrachloride, Kokorev et al. (1960) found a significant number of damaged respiratory pathways (hyperaemia, thinning of mucosa, toxic bronchitis). The author considered these effects were caused by titanium tetrachloride and the products of its hydrolysis.

8. EVALUATION OF HEALTH RISKS TO MAN

There is no evidence indicating that titanium is an essential element for man or animals. According to available data on the toxicity of titanium and titanium compounds and their presence in various environmental media, there is no reason to believe that exposure to titanium would constitute any health risks for the general population. Studies on titanium alloys, used in implants, do not indicate any adverse local effects on tissues, suggesting that titanium is a biologically compatible element.

Accidental exposure to titanium tetrachloride constitutes a hazard in industrial settings, as contact with either the substance or the fumes emitted will cause burns.

Occupational exposure to titanium dioxide occurs frequently and the level of exposure may be high. Studies on experimental animals, clinical studies including autopsies, as well as some epidemiological surveys on exposed working populations have shown convincingly that titanium dioxide is biologically inert and does not possess fibrogenic characteristics. This has been corroborated by in vitro investigations, where, however, different titanium dioxide dusts were shown to have various degrees of haemolytic activity, rutile being practically inert and anatase having a measurable haemolytic activity. This emphasizes the importance of considering titanium dioxide dusts of different composition and mineralogical structure separately, always stating clearly the characteristics of a tested compound.

In studies where fibrosis has been reported in association with exposure to titanium dioxide dusts, the etiological relationship has not been convincingly proved. Moreover, in these studies concomitant exposure to other elements such as silica seems to offer a more likely explanation of the fibrosis than the titanium dioxide itself.

Other titanium compounds, such as the hydride, carbide, and boride, may have fibrogenic properties according to experimental animal studies. Man-made fibres such as potassium octatitanate or titanium phosphate fibres are also fibrogenic in laboratory animals.

Available data do not suggest that titanium or titanium compounds induce any mutagenic or teratogenic effects. However, few studies on these aspects have been made. Intramuscular injection of powdered titanium metal has induced fibrosarcomas and lymphosarcomas in rats. Titanocene, an organotitanium compound, has induced fibrosarcomas in rats. Available data on the carcinogenicity of titanium in man do not indicate any such effect, and adverse immunological reactions to titanium have not been reported.

It is not possible from the available data to establish dose-effect or dose-response relationships for any effect associated with exposure to titanium or its compounds. Thus no quantitative assessment of the human health risk from exposure to titanium or titanium compounds in occupational or non-occupational environmental situations can be made.

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