TITANIUM DIOXIDE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 13463-67-7 - Titanium dioxide
1317-70-0 - Anatase titanium dioxide
1317-80-2 - Rutile titanium dioxide
Chem. Abstr. Name: Titanium dioxide
IUPAC Systematic Name: Titanium dioxide
Synonyms: CI 77891; E 171; NCI-CO4240; Pigment White 6; titania; titanium (IV) oxide

1.2 Molecular formula and molecular weight

TiO_2 Mol. wt: 79.90

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Fine white powder (Windholz, 1983); crystal structure is tetragonal with the titanium ion octahedrally bonded to six oxygen ions; position of octahedra in the lattice and number of molecules per unit cell differ for anatase and rutile forms: anatase titanium dioxide contains four molecules per unit cell, rutile contains only two (Schiek, 1982).

(*b*) *Density*: Anatase, 3.84 g/cm^3; rutile, 4.26 g/cm^3 (Weast, 1985)

(*c*) *Spectroscopy*: X-ray diffraction patterns for anatase and rutile titanium dioxide have been reported (Roberts *et al.*, 1974).

(*d*) *Refractive index*: Anatase, 2.554, 2.493; rutile, 2.616, 2.903 (Weast, 1985)

(*e*) *Solubility*: Soluble in sulfuric acid and alkalis; insoluble in water (Weast, 1985)

1.4 Technical products and impurities

Trade names: A-Fil Cream; Atlas white titanium dioxide; Austiox; Bayertitan; Calcotone White T; Cosmetic White C47-5175; Cosmetic White C47-9623; C-Weiss 7; Flamenco;

Hombitan; Horse Head A-410; Horse Head A-420; Horse Head R-710; KH 360; Kronos titanium dioxide; Levnox White RKB; Rayox; Runa RH20; Rutile; Tichlor; Tiofine; Tiona T.D.; Tioxide; Tipaque; Ti-Pure; Titafrance; Titandioxid; Titanox; Titanox 2010; Trioxide(s); Tronox; Unitane products (various); 1700 White; Zopaque

The technical products that incorporate titanium dioxide require a component that is essentially free from coloured impurities in order to produce the desired whitening and opacifying effect. International standards have been established for four types of titanium dioxide pigments. Type I (minimum, 94% titanium dioxide) is an anatase, freely chalking pigment used in white interior and exterior house paints, chalking being the formation of a layer of loose pigment powder on the surface of weathered paint film (Schurr, 1981). Type II (minimum, 92% titanium dioxide) is a rutile pigment with medium chalking resistance used in varying amounts in all types of interior paints, enamels and lacquers. Type III (minimum, 80% titanium dioxide) is also a rutile pigment with medium chalking resistance, used principally in alkyd and emulsion flat wall paints. Type IV (minimum, 80% titanium dioxide) is another rutile pigment, but with high chalking resistance; it is used in exterior paints and has excellent durability and gloss retention (American Society for Testing and Materials, 1988). Typical median particle sizes for anatase and rutile pigments range from 0.2–0.3 μm (LeSota, 1978; Schurr, 1981).

Aluminium, silicon and zinc oxides may be added to either form of the pigment to enhance specific properties such as increased dispersibility and ultraviolet light resistance. Titanium dioxide pigments must remain free of extenders such as barium sulfate, clay, magnesium silicate and calcium carbonate; however, the pigment may be extended by blending with anhydrous calcium sulfate (Lowenheim & Moran, 1975; American Society for Testing and Materials, 1988).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Titanium dioxide is the principal white pigment used commercially, due to its high refractive index, its ease of dispersion into a variety of matrices, and its inertness towards those matrices during processing and throughout product life (Considine, 1974).

Two main processes exist for making titanium dioxide pigments: the sulfate process and the chloride process. The sulfate process, the older of the two, was first used in Europe and the USA around 1930 and was the primary process until the early 1950s, when the chloride process was developed. By 1981, the chloride process accounted for approximately 78% of US production and by 1982 for 68% of world titanium dioxide pigment production (Considine, 1974; Lynd & Lefond, 1983).

In the sulfate process, rutile or anatase titanium dioxide is produced by digesting ilmenite (iron titanate) or titanium slag with sulfuric acid. The major concern in selecting the

starting material for use in the process is that it contain as little as possible of impurities such as chromium, vanadium, manganese, niobium and phosphorus, which impair pigment properties. Ilmenite containing as little as 40% titanium dioxide can be used to produce pigment-grade titanium dioxide. Titanium slag may also be used as the starting material. Slag is produced by smelting ilmenite in an electric furnace and typically contains about 70% titanium dioxide, although concentrations may reach 85% (Considine, 1974; Lowenheim & Moran, 1975; Lynd & Lefond, 1983). Some typical materials used for pigment production throughout the world are shown in Table 1.

The sulfate process is a batch process in which concentrated sulfuric acid is added to ground ilmenite or titanium slag in proportions of 1.5:1 (acid to ore). An organic flocculent or antimony oxide may be added to induce aggregation of suspended titanyl and iron sulfates into a solid porous cake. The cake is dissolved in a dilute acid solution to release the sulfate agglomeration into solution. If necessary, scrap iron is added to reduce iron [III] to iron [II]. Also during this step, small amounts of titanium [IV] are reduced to titanium [III] to prevent later oxidation of iron [II]. The solution is clarified by settling and filtration. The resulting mother liquor is concentrated and subjected to steam for 6 h. Seed crystals may be added to aid nucleation. About 95% of the titanium in the mother liquor is hydrolysed to titanium hydrate or metatitanic acid (H_2TiO_3), which is collected on a filter and washed. The final filter cake is calcined at 900–1000°C to form titanium dioxide. The product is ground, quenched and dispersed in water; the coarse particles are separated in the thickener, reground and filtered; and the cake is dried in a rotary steam dryer and pulverized. The resulting product is anatase titanium dioxide. The rutile form is made by seeding the mother liquor with rutile seed crystals and conditioning the precipitated pigment with phosphates, potassium, antimony, aluminium or zinc compounds prior to calcination. The recovery of pigment-grade titanium dioxide in sulfate process plants is approximately 80% (Lowenheim & Moran, 1975; Lynd & Lefond, 1983; Lynd, 1985).

The chloride process is a continuous process that requires ores with a high content of titanium dioxide or concentrates such as natural or synthetic rutile. Natural rutile contains approximately 95% titanium dioxide; synthetic rutile or ilmenite (iron titanate) concentrates must have a minimum titanium dioxide content of 60% to produce economical yields of pigment in this process. The titanium dioxide content in ilmenite may be increased by reducing iron to its elemental form, followed by chemical or physical separation. Another method of enrichment is reducing iron [III] to iron [II] and chemically leaching it out of the mineral. A third method involves prior selective chlorination to remove iron and other impurities (Considine, 1974; Lowenheim & Moran, 1975; Lynd & Lefond, 1983).

In the chloride process, ore is ground and mixed with coke in a fluidized or static bed reactor and chlorinated at temperatures of 850–1000°C. Titanium tetrachloride is produced, along with chlorides of impurities present in the starting material, which include chlorides of iron, vanadium and silicon; these are removed chemically and through fractional distillation. Hydrogen chloride and carbon dioxide are present after chlorination and are vented prior to fractional distillation. Conversion to titanium dioxide is accomplished by burning titanium tetrachloride with air or oxygen at temperatures of 1200–1370°C. The resulting fine-grained oxide is sometimes calcined at about 500–600°C to remove any residual

Table 1. Composition of typical commercial ilmenite concentrates and titaniferous slag[a] (weight percent)

Material	USA		Australia		Norway	India		Malaysia (Amang[c])	Canada (Québec)	South Africa (Richards Bay slag)
	New York	Florida	Company A	Company B		Quilon deposit	MK deposit[b]			
TiO_2 (total)	46.1	64.00	54.4	55.4	45.0	60.6	54.2	53.1	70–74	85.0 (min)
Ti_2O_3									10–15	25.0 (max)
Fe_2O_3	6.7	28.48	19.0	11.1	12.5	24.2	14.2	8.7		
FeO	39.3	1.33	19.8	22.5	34.0	9.3	26.6	33.6	12–15	
Al_2O_3	1.4	1.23	1.5		0.6	1.0	1.3		4–6	
SiO_2	1.5	0.28	0.7	1.4	2.8	0.7			3.5–5	
CaO	0.5	0.007	0.04		0.25				1.2 (max)	0.15 (max)
MgO	1.9	0.20	0.45		5.0	0.9	1.0		4.5–5.5	1.3 (max)
Cr_2O_3	0.009		0.2	0.03	< 0.076	0.12	0.07	0.005	0.25	0.3 (max)
V_2O_5	0.05		0.12	0.13	0.16	0.15	0.16	0.02	0.5–0.6	0.6 (max)
ZrO_2	0.01					0.9	0.8			
S	0.6		< 0.01		< 0.05	0.21	0.12		0.03–0.10	
P_2O_5	0.008	0.12	0.02		< 0.04			0.085	0.025 (max)	
MnO	0.5		1.4		0.25	0.4	0.4	4.0	0.2–0.3	2.5 (max)
H_2O (loss on ignition)	1.3		0.4			2.0	0.3			
Rare earths						trace	0.12			
C	0.22				< 0.055				0.03–0.10	

[a]From Lynd & Lefond (1983)

[b]MK, Manavalakwuchi area

[c]Amang, a crude mixture of heavy minerals that must be treated further to recover ilmenite

chlorine or hydrogen chloride. These gases are separated, and the chlorine is collected and recirculated to the chlorinator. Approximately 90% of the chlorine may be recycled. Aluminium chloride is added to titanium tetrachloride to assure near-total conversion to rutile titanium dioxide. A typical yield from this process is 90% (Lowenheim & Moran, 1975; Lynd & Lefond, 1983; Lynd, 1985).

Current worldwide demand for titanium dioxide is about 2.8 million tonnes (Anon., 1988a,b,c). Production volumes in 1978–86 in several countries are given in Table 2.

Table 2. Titanium dioxide pigment production by country in 1978–86 (thousand tonnes)[a]

Country	1978	1979	1980	1981	1982	1983	1984	1985	1986
Brazil	NA	NA	29.9	32.8	30.9	45.3	45.0	NA	NA
Czechoslavakia	19.1	18.8	16.6	16.7	20.0	21.0	20.4	NA	NA
Finland	NA	270.7	355.2	402.1	366.3	420.7	502.2	NA	NA
India	9.9	NA	NA	NA	NA	NA	NA	NA	NA
Italy[b]	60.0	59.0	–	–	–	–	–	–	–
Japan	171.4	185.4	172.8	176.2	184.0	195.9	204.7	217.7	222.9
Korea, Republic of	9.2	5.1	8.0	9.8	11.1	14.4	NA	NA	NA
Mexico	28.5	35.0	39.1	40.0	37.5	40.5	44.7	NA	NA
Spain	53.9	66.1	51.4	66.6	67.5	64.9	70.0	74.7	NA
UK	205.3	192.9	186.7	169.6	172.3	193.9	206.0	219.1	230.0
USA	635.8	673.1	659.4	690.2	598.6	689.3	757.3	780	844.7
USSR	7.1	7.1	6.0	4.7	5.0	5.0	6.4	NA	NA
Yugoslavia	19.2	19.6	19.6	21.9	21.4	25.6	21.7	NA	NA

[a]From Anon. (1988d,e); NA, not available
[b]Not produced after 1979

(b) Use

The principal use of titanium dioxide is as a whitening and opacifying agent in paints, varnishes, lacquers, paper, plastics, ceramics, rubber and printing ink (Table 3). These industries accounted for 93–95% of the titanium dioxide pigment used in the USA during 1982–86 (Mannsville Chemical Products Corp., 1983; Lynd & Hough, 1986).

Titanium dioxide is the most common white synthetic pigment used in the paint industry. Modern paint plants often handle titanium dioxide as a slurry for convenience and to avoid airborne particulates (Schurr, 1981). In the paper industry, both anatase and rutile titanium dioxides are used to improve opacity. The total amount of pigment varies with the grade of paper but may comprise 2–40% of the final sheet, of which as much as 25% may be titanium dioxide. The pigment is dispersed during the pulping process and retained in the sheet during formation with organic polymers. The optical efficiency of titanium pigment is improved by synthetic silicas and silicates (Baum *et al.*, 1981). Paper is waterproofed by coating the sheets with polyethylene resins whitened with titanium dioxide (Locker, 1982).

Table 3. Percent distribution of titanium dioxide pigment used within US industries, 1982–86[a]

Industry	1982	1983	1984	1985	1986
Paint, varnish, lacquer	48.1	48.9	54.8	54.3	52.6
Paper	27.4	27.3	19.9	20.5	20.7
Plastics	12.7	13.2	15.4	16.2	15.8
Ceramics	1.2	1.0	1.0	0.7	2.2
Rubber	2.6	1.8	2.0	1.7	2.0
Printing inks	1.0	1.1	1.2	1.0	1.4
Other	7.0	6.7	5.7	5.6	5.3

[a]From Lynd & Hough (1986)

Titanium oxide is incorporated into various plastic products to confer opacity and whiteness, and also because it resists degradation by ultraviolet light and is chemically inert (Lynd, 1985).

Commercial use of anatase titanium dioxide as an opacifier for ceramic and enamel products began in 1946. Rutile pigments may also be used for this purpose (Friedberg, 1980; Lynd, 1985).

Titanium dioxide is also incorporated into rubber tyres to make whitewall tyres (Lynd, 1985). In printing inks, titanium dioxide is mixed with coloured pigments to add opacity or lighten the hue. In a typical nitrocellulose ink formulation, titanium pigment is present at 35 wt%. An acrylic-based ink formulation contained 30 wt% titanium dioxide (Burachinsky *et al.*, 1981).

Other uses for titanium dioxide are as a catalyst in the production of alcohol fuels (Klass, 1984), as a delusterant in a variety of synthetic fibres at up to 2 wt% (Davis & Hill, 1982), as a component of flame-retardant formulations for wood (Wegner *et al.*, 1984), in cosmetics as a physical sunscreening agent (Isacoff, 1979), as a component of gums, resins and waxes used for making dental impressions (Paffenbarger & Rupp, 1979), and as a pigment in floor coverings, leather products and soaps (Mannsville Chemical Products Corp., 1983).

(c) *Regulatory status and guidelines*

Occupational exposure limits for titanium dioxide in 13 countries or regions are presented in Table 4.

Titanium dioxide may be used as a food colour additive with the following specifications limiting impurities: antimony compounds, < 100 mg/kg; zinc compounds, < 50 mg/kg; soluble barium compounds, < 5 mg/kg; and hydrochloric acid-soluble compounds, < 3.4 g/kg (Commission of the European Communities, 1962).

Table 4. Occupational exposure limits for titanium dioxide[a]

Country or region	Year	Concentration[b] (mg/m³)	Interpretation[c]
Austria	1985	8	TWA
Denmark	1988	6	TWA
Finland	1987	10	TWA
German Democratic Republic	1985	5	TWA
		10	STEL
Germany, Federal Republic of	1988	6[d]	TWA
Netherlands	1986	10	TWA
Norway	1981	10	TWA
Switzerland	1985	6	TWA
Taiwan	1985	S 10	TWA
UK	1987		
Total inhalable dust		10	TWA
Respirable dust		5	TWA
USA[e]			
OSHA	1985	15	TWA
ACGIH	1988	10[f]	TWA
USSR	1986	10	TWA
Venezuela	1985	20	Ceiling

[a]From Direktoratet for Arbeidstilsynet (1981); Arbeidsinspectie (1986); Institut National de Recherche et de Sécurité (1986); Cook (1987); Health and Safety Executive (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit

[d]Total dust containing no asbestos and < 1% free silica

[e]OSHA, Occupational Safety and Health Administration; ACGIH, American Conference of Governmental Industrial Hygienists

[f]Measured as fine dust

2.2 Occurrence

(a) *Natural occurrence*

Titanium dioxide occurs naturally in three crystalline forms: anatase, rutile and brookite. Only anatase and rutile are of commercial importance. Rutile can be mined directly, but anatase is obtained through the processing of ilmenite, a natural iron titanate (Lynd, 1985).

Rutile is a widespread accessory mineral found in high-grade metamorphic gneisses and schists and in igneous rocks. It also occurs in black sand deposits in many parts of the world. Typically, the composition of rutile is 95% titanium dioxide, the remaining 5% being silicon, chromium, vanadium, aluminium and iron oxides (Lynd & Lefond, 1983).

Ilmenite is a common accessory grain in igneous rocks such as anorthosites, gabbros and basic lavas; it may also occur as an intergrowth in magnetite and haematite. Weathering

and alterations along grain boundaries result in the removal of iron from the ilmenite lattice, producing leucoxene or pseudorutile. Ilmenite is also found in sand deposits (Lynd & Lefond, 1983).

The principal producing countries for rutile and ilmenite are Australia, Brazil, Canada, China, Finland, India, Malaysia, Mexico, Norway, Sierra Leone, South Africa, Sri Lanka and the USA (Lynd & Lefond, 1983).

(*b*) *Occupational exposure*

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 1 270 000 workers were potentially exposed to titanium dioxide in the USA in 1981–83.

Although it is apparent that occupational exposure to titanium dioxide is extensive, there are few data on levels and sources of exposure (Santodonato *et al.*, 1985), and the data available in the literature are reported as total dust or nuisance dust and not as titanium dioxide. Concentrations ranged from 10 to 400 mg/m^3 during the grinding of titanium dioxide pigment, but documentation of these levels was not provided (Elo *et al.*, 1972). Long-term exposures to titanium dioxide dust in a titanium pigment production factory occasionally exceeded 10 mg/m^3, and exposures greater than 10 mg/m^3 were common during the repair of production machinery (Rode *et al.*, 1981).

2.3 Analysis

No information was available to the Working Group on methods for the quantitative determination of titanium dioxide in environmental samples. Occupational exposures to titanium dioxide have been estimated gravimetrically as total or respirable dust (Lee *et al.*, 1986).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: Groups of 50 male and 50 female B6C3F1 mice, five weeks old, were fed diets containing 0, 2.5% or 5.0% titanium dioxide (anatase; purity, $\geq$98%) daily for 103 weeks. Mice were killed at 109 weeks of age, one week after exposure was stopped. At terminal sacrifice, there was no significant difference in survival between treated and control males: 32, 40 and 40 controls, low-dose and high-dose males were still alive at that time. In female mice, a dose-related trend for decreased survival was significant in treated groups (p = 0.001, Tarone test); survival at terminal sacrifice was 45, 39 and 33 among control, low-dose and high-dose females, respectively. No difference in body weights between treated and

control groups and no significant increase in the incidence of tumours was observed in treated mice of either sex (National Cancer Institute, 1979).

Rat: Groups of 50 male and 50 female Fischer 344 rats, nine weeks old, were fed diets containing 0, 2.5% or 5.0% titanium dioxide (anatase; purity, ≥98%) daily for 103 weeks. Rats were killed at 113 weeks of age, one week after exposure was stopped. There was no significant difference in survival between treated and control groups of either sex; survival of males at terminal sacrifice was 31, 37 and 36 among control, low-dose and high-dose groups, respectively, and that of females was 36, 36 and 34 in control, low-dose and high-dose groups, respectively. No difference in body weights between treated and control groups and no significant increase in the incidence of tumours was observed in treated mice of either sex (National Cancer Institute, 1979).

(*b*) *Inhalation/intratracheal administration*

Rat: Groups of 50 male and 50 female Sprague–Dawley rats, eight weeks of age, were exposed by inhalation to 0 or 15.95 mg/m^3 titanium dioxide [purity unspecified] for 6 h per day on five days per week for 12 weeks. After 140 weeks (128 weeks after the end of exposure), all surviving rats were sacrificed. Average survival was 116 and 113 weeks for control and treated males and 114 and 120 weeks for control and treated females, respectively. At terminal sacrifice, 39 control males, 44 treated males, 45 control females and 45 treated females were still alive. No difference in body weights between treated and control groups and no significant increase in the incidence of tumours was observed in treated mice of either sex (Thyssen *et al.*, 1978). [The Working Group noted the short duration of exposure and the relatively low exposure level.]

Groups of 100 male and 100 female CD rats, five weeks of age, were exposed by inhalation to 0, 10, 50 or 250 mg/m^3 titanium dioxide (rutile; 99% pure; 84% of dust particles of respirable size) for 6 h per day on five days per week for two years. At three, six and 12 months, five, five and ten rats of each sex at each dose, respectively, were removed for interim kills. No difference in mortality, body weight or clinical signs was observed. Nasal cavities were examined histologically, and no tumour was observed. Lung tumours were observed primarily in high-dose rats of each sex. The incidences of lung adenomas were: males – control, 2/79; low-dose, 1/71; mid-dose, 1/75; and high-dose, 12/77; females – control, 0/77; low-dose, 0/75; mid-dose, 0/74; and high-dose, 13/74. The incidences of cystic keratinizing squamous-cell carcinomas were: males – 0/79, 0/71, 0/75 and 1/77; females – 0/77, 1/75, 0/74 and 13/74. One anaplastic carcinoma occurred in a low-dose male. The lung tumours occurred in the bronchioloalveolar region, and no evidence of metastasis was observed. The authors noted difficulty in distinguishing between the squamous-cell carcinomas and keratinizing squamous metaplasia (Lee *et al.*, 1985a,b, 1986).

Hamster: Groups of 24 male and 24 female Syrian golden hamsters, six to seven weeks old, received intratracheal administrations of 0 or 3 mg titanium dioxide ([purity unspecified] particle size, 97% < 5 μm) in 0.2 ml saline once a week for 15 weeks. Animals were observed until spontaneous death and all control and treated hamsters died by 120 and 80 weeks, respectively, after the beginning of treatment. The respiratory tract and other organs with gross lesions were examined microscopically; no respiratory tract tumour occurred in treated

hamsters, but two tracheal papillomas were found in untreated controls (Stenbäck *et al.*, 1976).

(*c*) *Subcutaneous injection*

Rat: Groups of 20 male and 20 female Sprague–Dawley rats, 13 weeks old, received a single subcutaneous injection of 1 ml saline or 30 mg of one of three preparations of titanium dioxide (≥99%, ≥95% or ≥85% pure) in 1 ml saline into the flank. All rats were observed until spontaneous death, which occurred as late as 136, 126, 146 and 133 weeks in the control and titanium dioxide–treated groups, respectively. No tumour was observed at the site of the injection in any group (Maltoni *et al.*, 1982). [The Working Group noted the inadequate reporting of the study.]

(*d*) *Intraperitoneal injection*

Mouse: Groups of 30 or 32 male Marsh–Buffalo mice, five to six months old, received a single intraperitoneal injection of 0 or 25 mg titanium dioxide (purity, ≥98%; manually ground) in 0.25 ml saline. All survivors (ten control and 13 treated mice) were killed 18 months after treatment. No difference in the incidence of local or distant tumours was observed between treated and control animals (Bischoff & Bryson, 1982). [The Working Group noted the small number of animals used.]

Rat: As part of a large study on various dusts, three groups of female Wistar rats, nine, four and five weeks of age, received intraperitoneal injections of granular titanium dioxide [purity unspecified] in 2 ml 0.9% sodium chloride solution. The first group received a total dose of 90 mg per animal by five weekly injections; the second group received a single injection of 5 mg per animal; and the third group received three weekly injections of 2, 4 and 4 mg per animal. One concurrent group of 32 five-week-old Wistar rats received a single injection of saline alone. Average lifespans were 120, 102, 130 and 120 weeks. No intra-abdominal tumour was reported in 47 and 32 rats from the second and third groups that were examined; six of 113 rats examined from the first group had sarcomas, mesotheliomas or carcinomas of the abdominal cavity [numbers unspecified]. Two controls had abdominal tumours. In a similar experiment with female Sprague–Dawley rats given single intraperitoneal injections of 5 mg per animal titanium dioxide, 2/52 rats developed abdominal tumours (average lifespan, 99 weeks). Controls were not available for comparison (Pott *et al.*, 1987).

(*e*) *Administration with known carcinogens*

Hamster: Groups of 24 male and 24 female Syrian golden hamsters, six to seven weeks old, received intratracheal administrations of 3 mg titanium dioxide ([purity unspecified] particle size, 97% < 5 μm) plus benzo[*a*]pyrene in 0.2 ml saline, or benzo[*a*]pyrene in saline (controls) once a week for 15 weeks. Animals were observed until spontaneous death; all control and treated hamsters had died by 100 and 70 weeks, respectively. In the 48 hamsters [number of tumours per sex unspecified] treated with titanium dioxide plus benzo[*a*]pyrene, tumours occurred in the larynx (11 papillomas, five squamous-cell carcinomas), trachea (three papillomas, 14 squamous-cell carcinomas, one adenocarcinoma) and lung (one adenoma, one adenocarcinoma, 15 squamous-cell carcinomas, one anaplastic carcinoma). Two papillomas occurred in the larynx of benzo[*a*]pyrene–treated controls. In the same study,

ferric oxide and benzo[*a*]pyrene induced a similar spectrum of tumours as that induced by the combination with titanium dioxide; aluminium oxide and benzo[*a*]pyrene produced no increase in tumour incidence compared with benzo[*a*]pyrene–treated controls (Stenbäck *et al.*, 1976).

3.2 Other relevant data

(*a*) *Experimental systems*

The toxicology of titanium dioxide has been reviewed (World Health Organization, 1982).

(i) *Absorption, distribution, excretion and metabolism*

The pattern of deposition of titanium dioxide (anatase) dust in the lungs of rats was similar to that seen with other particles (Ferin *et al.*, 1983). After rats were exposed to 16.5 mg/m^3 anatase and 19.3 mg/m^3 rutile aerosols (mass median aerodynamic diameters, about 1 μm) for 7 h, the half-lives of pulmonary clearance were 51 and 53 days, respectively (Ferin & Oberdörster, 1985). Pulmonary clearance of titanium dioxide was significantly decreased after long-term exposure to 1 ppm (2.6 mg/m^3) sulfur dioxide (Ferin & Leach, 1973).

Following intratracheal instillation of titanium dioxide to mice and rapid partial removal of particles by ciliary clearance within the first 15 min, subsequent pulmonary clearance had a half-life of about 20 days; the slow phase was assumed to be due to uptake of the particles and removal by macrophages (Finch *et al.*, 1987).

After exposure of rats by inhalation to 10, 50 and 250 mg/m^3 titanium dioxide (rutile; mass median aerodynamic diameter, 1.5–1.7 μm) for 6 h per day on five days per week for two years, inhaled particles were found to be engulfed by macrophages, and dense accumulation of dust-laden macrophages was seen in perivascular and peribronchial lymphoid tissue. Massive accumulation of these dust-containing cells was also seen in tracheobronchial lymph nodes and, to a lesser extent, in cervical lymph nodes. The occurrence of dust particles in mesenteric lymph nodes, in the liver and in the spleen suggests that small amounts could have entered the general circulation from the lungs (Lee *et al.*, 1985a). Also after intravenous injection to rats, titanium dioxide particles were found to accumulate in abdominal lymph nodes (coeliac nodes) which drain the liver (Huggins & Froehlich, 1966). Pulmonary accumulation increased considerably in rats exposed by inhalation to 250 mg/m^3 as compared to 10 and 50 mg/m^3, indicating that pulmonary clearance mechanisms can be overloaded at the highest dose (Lee *et al.*, 1986).

(ii) *Toxic effects*

Titanium dioxide pigments (anatase and others) caused significant mobilization of peritoneal macrophages when injected into the peritoneal cavity of mice (Nuuja *et al.*, 1982). They decreased the level of acid phosphatase in mouse peritoneal macrophages *in vitro*; silica-coated particles were the most effective (Nuuja & Arstila, 1982). In both studies, titanium dioxide had minimal cytotoxicity in comparison to quartz and asbestos. *In vivo*, titanium dioxide (anatase and rutile) failed to induce proline hydroxylase in the lungs of rats four weeks after they had been exposed by inhalation (Zitting & Skyttä, 1979).

Anatase, rutile and rutile containing trace amounts of nickel or chromium had no fibrotic potential in either an in-vitro test for cell viability using bovine alveolar macrophages or following instillation into rat lungs *in vivo*; α-quartz gave positive results in both assays (Richards *et al.*, 1985). Similarly, injection of an untreated anatase form of titanium dioxide (particle size, 0.8–16 μm) into the pleura of rats caused no pleural effusion and only a few strands of connective tissue surrounding the collections of macrophages (Grasso *et al.*, 1983). Additional studies *in vivo* have all failed to demonstrate any fibrotic potential in rats or rabbits (Grandjean *et al.*, 1956; Christie *et al.*, 1963; Dale, 1973; Sethi *et al.*, 1973; Ferin & Oberdörster, 1985); however, one study showed that intratracheal instillations of 3 mg titanium dioxide to hamsters once a week for 15 weeks resulted in slight pulmonary inflammation and, subsequently, interstitial fibrosis (Stenbäck *et al.*, 1976). Inflammatory changes and formation of collagen fibres were also seen after intratracheal instillation into rats of ilmenite (iron titanate) or titanium dioxide dusts (Shevtsova, 1968).

Following overloading of lung clearance in rats exposed to 250 mg/m^3 rutile for 6 h per day on five days per week for two years, there was massive accumulation of dust-laden macrophages; free particles and cellular debris were found in the alveoli, and alveolar proteinosis and cholesterol granulomas developed. Lung weights increased, and white patches of accumulated dusts were seen in the lungs at autopsy (Lee *et al.*, 1985b, 1986).

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

Titanium dioxide did not induce differential killing in DNA repair-proficient compared to repair-deficient strains of *Bacillus subtilis* rec$^{+/-}$ [details not given] (Kada *et al.*, 1980).

Titanium dioxide was not mutagenic to *Salmonella typhimurium* TA1535, TA1537, TA1538, TA97, TA98 or TA100 (Dunkel *et al.*, 1985; Zeiger *et al.*, 1988) or to *Escherichia coli* WP2, either in the presence or absence of an exogenous metabolic system from the livers of uninduced and Aroclor-induced rats, mice and Syrian hamsters (Dunkel *et al.*, 1985).

It did not induce morphological transformation in Syrian hamster embryo cells (Di Paolo & Casto, 1979) and did not enhance transformation of Syrian hamster embryo cells by the SA7 adenovirus (Casto *et al.*, 1979).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

Pulmonary retention of titanium dioxide dusts has been documented in several studies. The lungs usually contain higher levels of titanium than any other organ analysed (Schroeder *et al.*, 1963). In lung tissue obtained from one autopsy and two thoracotomies performed on workmen employed in a factory that processed titanium dioxide, titanium dioxide was found in lysosomes of alveolar macrophages and in lymphatic macrophages (Elo *et al.*, 1972). Dust-laden macrophages were seen in sputum samples from current titanium dioxide workers and from retired workers who had left the factory three years earlier; in lung biopsies from retired workers, macrophages were loaded with titanium dioxide and with silicon, which possi-

bly originated from the titanium dioxide coating (Määttä & Arstila, 1975). Massive deposition of rutile was also reported at autopsy in the lungs of a man who had been employed at a titanium dioxide production plant until four years before his death (Rode *et al.*, 1981). Titanium dioxide deposition has also been reported in regional lymph nodes (Schmitz-Moormann *et al.*, 1964; Yamadori *et al.*, 1986).

The pattern of regional deposition of titanium dioxide in the lungs and the relative contents in lymph nodes suggest that titanium dioxide is removed relatively slowly *via* the lymphatic system. The lungs of 35 miners contained an average of 71 mg titanium dioxide, but a total of only 4 mg was found in the regional lymph nodes (Einbrodt & Liffers, 1968).

(ii) *Toxic effects*

At an ilmenite (iron titanate) extraction plant, where workers were also exposed to rutile, chest X-rays (70 mm) were abnormal in 3/136 workers, of whom 24 had had more than ten years' exposure. The prevalence was similar to that (4/170) seen in a control group (Uragoda & Pinto, 1972). [The Working Group noted that the X-ray technique used would have detected only cases with severe pneumoconiosis.]

A man who was employed to pack titanium dioxide into cans developed pneumoconiosis after nine years of exposure; lung tissue examined five years later revealed slight fibrosis of interstitial tissue surrounding bronchioles and alveolar spaces (Yamadori *et al.*, 1986). In a study of lung tissue obtained from an autopsy and from two thoracotomies performed on titanium dioxide workers, deposits of titanium dioxide in interstitial lung tissue were also associated with cell destruction and slight fibrosis (Elo *et al.*, 1972). Määttä and Arstila (1975) suggested that the fibrogenic effect might be due to the presence of silicon compounds associated with the titanium dioxide dust. Another worker in titanium pigment production, however, had massive deposition of rutile in the lungs but no inflammation or fibrosis (Rode *et al.*, 1981). The absence of fibrotic changes has also been reported in a case after 15 years of exposure at a titanium dioxide mill (Schmitz-Moormann *et al.*, 1964).

As reported in an abstract, in a cross-sectional study of 207 workers producing titanium dioxide from ilmenite ore, the predominant signs were obstructive airway changes. In 26 workers, chest X-rays showed irregular or nodular opacities of limited extent; eight of these workers were known also to have been exposed to silica or asbestos (Daum *et al.*, 1977). [The Working Group noted that when titanium dioxide is produced from ilmenite ore the dried ore is digested by sulfuric acid, causing exposure to both sulfuric acid mist and titanium dioxide dust. The possible role of titanium dioxide could not be assessed.]

In a cross-sectional study of 209 titanium metal production workers, including 78 workers involved in the reduction process who were exposed to titanium tetrachloride vapour, titanium oxychloride and titanium dioxide particles, reductions in lung function (forced expiratory volume in one minute) were found. The authors noted that this finding could be due to exposure to titanium tetrachloride, which reacts violently with water to liberate heat and produce hydrochloric acid, titanium oxychloride and titanium dioxide. Pleural disease with plaques and pleural thickening was observed in 36 of the 209 workers, including eight of the 78 reduction process workers. Some cases were probably caused by prior exposure to asbestos; however, among workers not known to have been exposed to asbestos, the risk for pleu-

ral disease after more than ten years of employment was 3.8 times the risk in those who had been employed for fewer than five years. The authors noted that past exposure to asbestos at the titanium production facility may have contributed to the risk (Garabrant *et al.*, 1987).

A chest X-ray study of 336 workers at two titanium dioxide-producing plants showed 19 cases of pleural abnormalities (thickening/plaques), as compared to 3/62 among unexposed workers at the same plants. The odds ratio for chest X-ray abnormality associated with titanium dioxide exposure was 1.4. No lung fibrosis was observed. Exposures at the plants included titanium tetrachloride, potassium titanate and asbestos (Chen & Fayerweather, 1988).

A case of granulomatous lung disease was reported in a worker with possible exposure to titanium dioxide at an aluminium smelting plant where he worked near a firebrick furnace. A lymphocyte transformation test showed proliferative response to titanium chloride but not to any other metal tested, suggesting a possible link with titanium hypersensitivity (Redline *et al.*, 1986).

(iii) *Effects on fertility and on pregnancy outcome*

No data were available to the Working Group.

(iv) *Genetic and related effects*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

Titanium dioxide was found in the lungs of three patients who died of cancers at various sites (Schmitz-Moormann *et al.*, 1964; Ophus *et al.*, 1979; Rode *et al.*, 1981; Yamadori *et al.*, 1986), one of which was a papillary adenocarcinoma in the right lung. The latter had been engaged in packing titanium dioxide for about 13 years prior to his death at the age of 53 and had smoked about 17 cigarettes per day for 40 years; he had been diagnosed at the age of 48 as having pneumoconiosis.

Chen and Fayerweather (1988) studied mortality and cancer incidence among 1576 male employees who had been exposed to titanium dioxide for more than one year in two plants in the USA. Information on cancer incidence was obtained from the company cancer registry, which was started in 1956. Information on deaths among active and pensioned employees was obtained from the company mortality registry, which was started in 1957: vital status was determined for about 94% of the cohort, and death certificates were available for about 94% of those known to be deceased. Observed numbers of incident cancer cases were compared with expected numbers based on company rates, and the observed numbers of deaths were compared with both company and US rates. Mortality from all cancers was lower than expected. For lung cancer, nine deaths were observed, with 17.3 expected on the basis of national rates (standardized mortality ratio (SMR), 52; [95% confidence interval, 24–99]) and 15.3 expected on the basis of company rates (59; [27–112]). There was a slight excess of incident cancer cases, 38 *versus* 32.6 (117; [83–160]), due mainly to ten cases of tumours of the genitourinary system *versus* 6.3 expected (159; [76–292]); there were eight cases of lung cancer with 7.7 expected (104; [45–205]). [The Working Group noted that details of

exposure to titanium dioxide and other factors were not described, that cancer mortality and specific cancer sites were not reported in detail, that incident cancer cases only in actively employed persons were used for both observed and company reference rates, and that the numbers of incident cases were compared only with company rates.]

4. Summary of Data Reported and Evaluation

4.1 Exposures

Titanium dioxide is a white pigment produced mainly from ilmenite (iron titanate) and natural rutile (titanium dioxide). It is widely used in paints, paper, plastics, ceramics, rubber, inks and a variety of other products. Occupational exposure to titanium dioxide during its production, the production of paints, in painting trades and during other industrial use is likely to be extensive, but there is a paucity of data on levels, both occupational and environmental.

4.2 Experimental carcinogenicity data

Titanium dioxide was tested for carcinogenicity by oral administration in one strain of mice and in one strain of rats, by inhalation in two strains of rats, by intratracheal administration in one strain of hamsters, by subcutaneous injection in one strain of rats and by intraperitoneal administration in one strain of male mice and two strains of female rats. Increased incidences of lung adenomas in rats of both sexes and of cystic keratinizing lesions diagnosed as squamous-cell carcinomas in female rats were observed in animals that had inhaled the high but not the low doses of titanium dioxide. Oral, subcutaneous, intratracheal and intraperitoneal administration did not produce a significant increase in the frequency of any type of tumour in any species. Intratracheal administration of titanium dioxide in combination with benzo[*a*]pyrene to hamsters resulted in an increase in the incidence of benign and malignant tumours of the larynx, trachea and lungs over that in benzo[*a*]pyrene-treated controls.

4.3 Human carcinogenicity data

The only available epidemiological study provided inconclusive results.

4.4 Other relevant data

Titanium dioxide did not induce morphological transformation in mammalian cells or mutation in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

There is *inadequate evidence* for the carcinogenicity of titanium dioxide in humans.

There is *limited evidence* for the carcinogenicity of titanium dioxide in experimental animals.

Overall evaluation

Titanium dioxide *is not classifiable as to its carcinogenicity to humans (Group 3).*

5. References

American Conference of Governmental Industrial Hygienists (1988) *Threshold Limit Values and Biological Exposure Indices for 1988–1989*, Cincinnati, OH, p. 36

American Society for Testing and Materials (1988) Standard specification for titanium dioxide pigments. In: Storer, R.A., Cornillit, J.L., Savini, D.F., Hart, S.H., Richardson, D., O'Brien, K.W., Stanton, A.L., Loux, L.A., Craig, R.E., Fanelle, C.S., Fazio, P.C., Winfree, M.S., Gutman, E.L., McGee, P.A., Wise, C.J. & Shupak, H.J., eds, *1988 Annual Book of ASTM Standards: Paint–Pigments, Resins, and Polymers*, Philadelphia, PA, pp. 100–101

Anon. (1988a) TiO_2 makers move to balance market. *Chem. Mark. Rep., 234*, 3, 29–30

Anon. (1988b) Prime pigments - titanium dioxide. *Chem. Mark. Rep., 234*, 30

Anon. (1988c) NL boosting TiO_2 stake with grassroots plant in US. *Chem. Mark. Rep., 234*, 3

Anon. (1988d) Facts & figures for the chemical industry. *Chem. Eng. News, 66*, 34–82

Anon. (1988e) *CHEM–INTELL Database*, Chemical Intelligence Service, Dunstable, UK, Reed Telepublishing Limited

Arbeidsinspectie (Labour Inspection) (1986) *De Nationale MAC–Lijst 1986* [National MAC-list 1986] (*P145*), Voorburg, Ministry of Social Affairs and Work Inspection, p. 21

Arbejdstilsynet (Labour Inspection) (1988) *Graensevaerdier for Stoffer og Materialer* [Limit Values for Materials] (*At–anvisning No. 2.1.0.2*), Copenhagen, p. 31

Baum, G.A., Malcolm, E.W., Wahren, D., Swanson, J.W., Easty, D.B., Litvay, J.D. & Dugal, H.S. (1981) Paper. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 16, New York, John Wiley & Sons, pp. 777–778

Bischoff, F. & Bryson, G. (1982) Tissue reaction to and fate of parenterally administered titanium dioxide. I. The intraperitoneal site in male Marsh–Buffalo mice. *Res. Commun. chem. Pathol. Pharmacol., 38*, 279–290

Burachinsky, B.V., Dunn, H. & Ely, J.K. (1981) Inks. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, NY, John Wiley & Sons, pp. 377, 391

[1]For definitions of the italicized terms, see Preamble, pp. 27–30.

Casto, B.C., Meyers, J. & DiPaolo, J.A. (1979) Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res., 39*, 193–198

Chen, J.L. & Fayerweather, W.E. (1988) Epidemiologic study of workers exposed to titanium dioxide. *J. occup. Med., 30*, 937–942

Christie, H., MacKay, R.J. & Fisher, A.M. (1963) Pulmonary effects of inhalation of titanium dioxide by rats. *Am. ind. Hyg. Assoc. J., 24*, 42–46

Commission of the European Communities (1962) Council Directive concerning the uniformity of regulations of member states concerning colouring agents that could be used in food products for human consumption. *Off. J. Eur. Commun., 115*, 2645–2664

Considine, D.M. (1974) *Chemical and Process Technology Encyclopedia*, New York, McGraw-Hill, pp. 1102–1104

Cook, W.A. (1987) *Occupational Exposure Limits – Worldwide*, Washington DC, American Industrial Hygiene Association

Dale, K. (1973) Early effects of quartz and titanium dioxide dust on pulmonary function and tissue. An experimental study on rabbits. *Scand. J. respir. Dis., 54*, 168–184

Daum, S., Anderson, H.A., Lilis, R., Lorimer, W.V., Fischbein, S.A., Miller, A. & Selikoff, I.J. (1977) Pulmonary changes among titanium workers (Abstract). *Proc. R. Soc. Med., 70*, 31–32

Davis, G.W. & Hill, E.S. (1982) Polyester fibers. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 18, New York, John Wiley & Sons, p. 531

Deutsches Forschungsgemeinschaft (German Research Society) (1988) *Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte 1988* [Maximal Concentrations in the Workplace and Biological Tolerance Values for Working Materials 1986] (*Report No. XXIV*), Weinheim, VCH Verlagsgesellschaft, p. 58

Di Paolo, J.A. & Casto, B.C. (1979) Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic metal salts. *Cancer Res., 39*, 1008–1013

Direktoratet for Arbeidstilsynet (Directorate for Labour Inspection) (1981) *Administrative Normer for Forurensning i Arbeidsatmosfaere 1981* [Administrative Norms for Pollution in Work Atmosphere] (*No. 361*), Oslo, p. 21

Dunkel, V.C., Zeiger, E., Brusick, D., McCoy, E., McGregor, D., Mortelmans, K., Rosenkranz, H.S. & Simmon, V.F. (1985) Reproducibility of microbial mutagenicity assays. II. Testing of carcinogens and noncarcinogens in *Salmonella typhimurium* and *Escherichia coli*. *Environ. Mutagenesis, 7* (Suppl. 5), 1–248

Einbrodt, H.J. & Liffers, R. (1968) Studies of lymphatic transport of titanium dioxide from human lung (Ger.). *Arch. Hyg., 152*, 2–6

Elo, R., Määttä, K., Uksila, E. & Arstila, A.U. (1972) Pulmonary deposits of titanium dioxide in man. *Arch. Pathol., 94*, 417–424

Ferin, J. & Leach, L.J. (1973) The effect of SO_2 on lung clearance of TiO_2 particles in rats. *Am. ind. Hyg. Assoc. J., 34*, 260–263

Ferin, J. & Oberdörster, G. (1985) Biological effects and toxicity assessment of titanium dioxides: anatase and rutile. *Am. ind. Hyg. Assoc. J., 46*, 69–72

Ferin, J., Mercer, T.T. & Leach, L.J. (1983) The effect of aerosol charge on the deposition and clearance of TiO_2 particles in rats. *Environ. Res., 31*, 148–151

Finch, G.L., Fisher, G.L. & Hayes, T.L. (1987) The pulmonary effects and clearance of intratracheally instilled Ni_3S_2 and TiO_2 in mice. *Environ. Res., 42*, 83–93

Friedberg, A.L. (1980) Enamels, porcelain or vitreous. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 9, New York, John Wiley & Sons, pp. 14–15

Garabrant, D.H., Fine, L.J., Oliver, C., Bernstein, L. & Peters, J.M. (1987) Abnormalities of pulmonary function and pleural disease among titanium metal production workers. *Scand. J. Work Environ. Health, 13*, 47–51

Grandjean, E., Turrian, H. & Nicod, J.L. (1956) The fibrogenic action of quartz dusts. Biological methods for their quantitative evaluation in rats. *Arch. ind. Health, 14*, 426–441

Grasso, P., Mason, P.L., Cameron, W.M. & Sharratt, M. (1983) Tissue reaction to the intrapleural injection of polyvinyl chloride powder, α–quartz and titanium dioxide. *Ann. occup. Hyg., 27*, 415–425

Health and Safety Executive (1987) *Occupational Exposure Limits, 1987 (Guidance Note EH 40–87)*, London, Her Majesty's Stationery Office, p. 21

Huggins, C.B. & Froehlich, J.P. (1966) High concentration of injected titanium dioxide in abdominal lymph nodes. *J. exp. Med., 124*, 1099–1105

Institut National de Recherche et de Sécurité (National Institute for Research and Safety) (1986) *Valeurs Limites pour les Concentrations des Substances Dangereuses Dans l'Air des Lieux de Travail* [Limit Values for the Concentrations of Toxic Substances in the Air of Work Places] (*ND 1609–125–86*), Paris, p. 579

Isacoff, H. (1979) Cosmetics. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 7, New York, John Wiley & Sons, p. 152

Kada, T., Hirano, K. & Shirasu, Y. (1980) Screening of environmental chemical mutagens by the rec-assay system with *Bacillus subtilis*. *Chem. Mutagens, 6*, 149–173

Klass, D.L. (1984) Alcohol fuels. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technoplogy*, 3rd ed., Suppl., New York, John Wiley & Sons, p. 19

Lee, K.P., Trochimowicz, H.J. & Reinhardt, C.F. (1985a) Transmigration of titanium dioxide (TiO_2) particles in rats after inhalation exposure. *Exp. mol. Pathol., 42*, 331–343

Lee, K.P., Trochimowicz, H.J. & Reinhardt, C.F. (1985b) Pulmonary response of rats exposed to titanium dioxide (TiO_2) by inhalation for two years. *Toxicol. appl. Pharmacol., 79*, 179–192

Lee, K.P., Henry, N.W., III, Trochimowicz, H.J. & Reinhardt, C.F. (1986) Pulmonary response to impaired lung clearance in rats following excessive TiO_2 dust deposition. *Environ. Res., 41*, 144–167

LeSota, S. (1978) *Paint/Coatings Dictionary*, Philadelphia, PA, Federation of Societies for Coatings Technology, p. 424

Locker, D.J. (1982) Photography. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 17, New York, John Wiley & Sons, pp. 629–630

Lowenheim, F.A. & Moran, M.K. (1975) *Faith, Keyes, and Clark's Industrial Chemicals*, 4th ed., New York, John Wiley & Sons, pp. 814–821

Lynd, L.E. (1985) Titanium. In: *Mineral Facts and Problems (Bureau of Mines Bulletin 675)*, Washington DC, US Government Printing Office, pp. 1–21

Lynd, L.E. & Hough, R.A. (1986) Titanium. In: *Bureau of Mines Mineral Yearbook*, Vol. 1, Washington DC, Bureau of Mines, pp. 1–17

Lynd, L.E. & Lefond, S.J. (1983) Titanium minerals. In: Lefond, S.J., Bates, R., Bradbury, J.C., Buie, B.F., Foose, R.M., Hoy, R.B., Husted, J.E., McCarl, H.N., Roe, L., Rooney, L.F. & Stokowski, S., eds, *Industrial Minerals and Rocks (Nonmetallics other than Fuels)*, 5th ed., Vol. 2, New York, Society of Mining Engineers of the American Institute of Mining, Metallurgical and Petroleum Engineers, Inc., pp. 1303–1362

Määttä, K. & Arstila, A.U. (1975) Pulmonary deposits of titanium dioxide in cytologic and lung biopsy specimens. Light and electron microscopic X-ray analysis. *Lab. Invest., 33*, 342–346

Maltoni, C., Morisi, L. & Chieco, P. (1982) Experimental approach to the assessment of the carcinogenic risk of industrial inorganic pigments. In: Englund, A., Ringen, K. & Mehlman, M.A., eds, *Advances in Modern Environmental Toxicology*, Vol. 2, *Occupational Health Hazards of Solvents*, Princeton, NJ, Princeton Scientific Publishers, pp. 77–92

Mannsville Chemical Products Corp. (1983) *Chemical Products Synopsis: Titanium Dioxide*, Cortland, NY

National Cancer Institute (1979) *Bioassay of Titanium Dioxide for Possible Carcinogenicity (Tech. Rep. Ser. No. 97)*, Bethesda, MD

National Institute for Occupational Safety and Health (1983) *US National Occupational Exposure Survey, 1981–83*, Cincinnati, OH

Nuuja, I.J.M. & Arstila, A.U. (1982) On the response of mouse peritoneal macrophages to titanium dioxide pigments *in vitro*. *Environ. Res., 29*, 174–184

Nuuja, I.J.M., Ikkala, J., Määttä, K. & Arstila, A.U. (1982) Effects of titanium dioxide pigments on mouse peritoneal macrophages *in vivo*. *Bull. environ. Contam. Toxicol., 28*, 208–215

Ophus, E.M., Rode, L.E., Gylseth, B., Nicholson, D.G. & Saeed, K. (1979) Analysis of titanium pigments in human lung tissue. *Scand. J. Work Environ. Health, 5*, 290–296

Paffenbarger, G.C. & Rupp, N.W. (1979) Dental materials. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 7, New York, John Wiley & Sons, pp. 507, 512

Pott, F., Ziem, U., Reiffer, F.-J., Huth, F., Ernst, H. & Mohr, U. (1987) Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp. Pathol., 32*, 129–152

Redline, S., Barna, B., Tomashefski, J.F., Jr & Abraham, J.L. (1986) Granulomatous disease associated with pulmonary deposition of titanium. *Br. J. ind. Med., 43*, 652–656

Richards, R.J., White, L.R. & Eik-Nes, K.B. (1985) Biological reactivity of different crystalline forms of titanium dioxide *in vitro* and *in vivo*. *Scand. J. Work Environ. Health, 11*, 317–320

Roberts, W.L., Rapp, G.R., Jr & Weber, J. (1974) *Encyclopedia of Minerals*, New York, Van Nostrand Reinhold, pp. 21–22, 530

Rode, L.E., Ophus, E.M. & Gylseth, B. (1981) Massive pulmonary deposition of rutile after titanium dioxide exposure. Light-microscopical and physico-analytical methods in pigment identification. *Acta pathol. microbiol. scand., A89*, 455–461

Santodonato, J., Bosch, S., Meylan, W., Becker, J. & Neal, M. (1985) *Monograph on Human Exposure to Chemicals in the Workplace: Titanium Dioxide (Report No. SRC-TR-84-804)*, Syracuse, NY, Center for Hazard Assessment, Syracuse Research Corporation

Schiek, R.C. (1982) Pigments (inorganic). In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 17, New York, John Wiley & Sons, pp. 793–801

Schmitz-Moormann, P., Hörlein, H. & Hanefeld, F. (1964) Lung alterations after titanium dioxide dust exposure (Ger.). *Beitr. Silikoseforsch., 80*, 1–17

Schroeder, H.A., Balassa, J.J. & Tipton, I.H. (1963) Abnormal trace metals in man: titanium. *J. chron. Dis.*, *16*, 55–69

Schurr, G.G. (1981) Paint. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 16, New York, John Wiley & Sons, p. 742

Sethi, S., Hilscher, W. & Flasbeck, R. (1973) Tissue response to a single intraperitoneal injection of various substances in rats. *Zbl. Bakt. Hyg., I. Abt. Orig. B*, *157*, 131–144

Shevtsova, V.M. (1968) Data on the effect of titanium and zirconium ore dust on workers and on animals in chronic experiments (Russ.). *Gig. Tr. prof. Zabol.*, *12*, 24–29

Stenbäck, F., Rowland, J. & Sellakumar, A. (1976) Carcinogenicity of benzo[*a*]pyrene and dusts in the hamster lung (instilled intratracheally with titanium oxide, aluminium oxide, carbon and ferric oxide). *Oncology*, *33*, 29–34

Thyssen, J., Kimmerle, G., Dickhaus, S., Emminger, E. & Mohr, U. (1978) Inhalation studies with polyurethane foam dust in relation to respiratory tract carcinogenesis. *J. environ. Pathol. Toxicol.*, *1*, 501–508

Työsuojeluhallitus (National Finnish Board of Occupational Safety and Health) (1987) *HTP–Arvot 1987* [TLV Values 1987] (*Safety Bulletin No. 25*), Helsinki, Valtion Painatuskeskus, p. 14

Uragoda, C.G. & Pinto, M.R.M. (1972) An investigation into the health of workers in an ilmenite extracting plant. *Med. J. Aust.*, *1*, 167–169

Weast, R.C., ed. (1985) *Handbook of Chemistry and Physics*, 66th ed., Cleveland, OH, CRC Press, pp. B-154–B-155

Wegner, T.H., Baker, A.J., Bendtsen, B.A., Brenden, J.J., Eslyn, W.E., Harris, J.F., Howard, J.L., Miller, R.B., Pettersen, R.C., Rowe, J.W., Rowell, R.M., Simpson, W.T. & Zinkel, D.F. (1984) Wood. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, N., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 24, New York, John Wiley & Sons, pp. 594–595

Windholz, M., ed. (1983) *The Merck Index*, 10th ed., Rahway, NJ, Merck 26, p. 1356

World Health Organization (1982) *Titanium* (*Environmental Health Criteria 24*), Geneva

Yamadori, I., Ohsumi, S. & Taguchi, K. (1986) Titanium dioxide deposition and adenocarcinoma of the lung. *Acta pathol. jpn.*, *36*, 783–790

Zeiger, E., Anderson, S., Haworth, S., Lawlor, T. & Mortelmans, K. (1988) *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. mol. Mutagenesis*, *11* (*Suppl. 12*), 1–158

Zitting, A. & Skyttä, E. (1979) Biological activity of titanium dioxides. *Int. Arch. occup. environ. Health*, *43*, 93–97