

TITANIUM DIOXIDE

(Group 2B)

[The text of these Summaries and Evaluations may be edited for language and clarity during the checking of the main text of the Monographs.]

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5. Summary of Data Reported

5.1 Exposure data

Titanium dioxide was first produced commercially in 1923 and accounts for approximately 70% of the total volume of pigment production. Relatively small quantities of titanium dioxide are used for non-pigmentary purposes. In 2004, worldwide production of titanium dioxide was 4.4 million tonnes.

Titanium dioxide is obtained from a variety of ores that contain ilmenite, rutile, anatase and leucosene, which are mined from deposits located throughout the world. Most titanium dioxide pigment is produced from titanium mineral concentrates by the chloride or sulfate process, either as the rutile or the anatase form. The primary particles are typically between 0.2 and 0.3 μm in diameter, although larger aggregates and agglomerates are formed. Ultrafine grades of titanium dioxide have a primary particle size of 10–50 nm and are used predominantly as ultraviolet blockers in sunscreens and plastics, and in catalysts. Most commercial titanium dioxide products are coated with inorganic (e.g. alumina, zirconia, silica) and organic (e.g. polyols, esters, siloxanes, silanes) compounds to control and improve surface properties.

Levels of occupational exposure to titanium dioxide during its manufacture have been reported from the USA and Europe between 1970 and 2000. The highest levels of exposure were observed during packing and milling, although high exposure also occurred in occupations such as site cleaning and maintenance. Levels of exposure to respirable dust in these occupations ranged between < 1 and 5 mg/m^3 (geometric mean) but have declined over time. No data were available that would allow the characterization or quantification of exposure to ultrafine primary particles. Workers in the titanium dioxide manufacturing industry may also be exposed to ore and other dusts, strong acids and asbestos.

Exposure to titanium dioxide in user industries is difficult to estimate and characterize due to the paucity of data. However, exposure levels are assumed to be lower in the user industries, with the possible exception of workers who handle large quantities of titanium dioxide. No significant exposure to titanium dioxide is thought to occur during the use of products in which titanium dioxide is bound to other materials, such as in paints.

5.2 Human carcinogenicity data

Three epidemiological cohort studies and one population-based case–control study from North America and western Europe were available for evaluation.

The largest of the cohort studies was among white male production workers in the titanium dioxide industry in six European countries. The study indicated a slightly increased risk for lung cancer compared with the general population. However, there was no evidence of an exposure–response relationship within the cohort. No increase in the mortality rates for kidney cancer was found when the cohort was compared with the general population, but there was a suggestion of an exposure–response relationship in internal analyses. The other cohort studies, both of which were conducted in the USA, did not report an increased risk for lung cancer or cancer at any other site; no results for kidney cancer were reported, presumably because there were few cases.

One population-based case–control study conducted in Montreal did not indicate an increased risk for lung or kidney cancer.

In summary, the studies do not suggest an association between occupational exposure to titanium dioxide as it occurred in recent decades in western Europe and North America and risk for cancer.

All the studies had methodological limitations; misclassification of exposure could not be ruled out. None of the studies was designed to assess the impact of particle size (fine or ultrafine) or the potential effect of the coating compounds on the risk for lung cancer.

5.3 Animal carcinogenicity data

Pigmentary and ultrafine titanium dioxide were tested for carcinogenicity by oral administration in mice and rats, by inhalation in rats and female mice, by intratracheal administration in hamsters and female rats and mice, by subcutaneous injection in rats and by intraperitoneal administration in male mice and female rats.

In one inhalation study, the incidence of benign and malignant lung tumours was increased in female rats. In another inhalation study, the incidences of lung adenomas were increased in the high-dose groups of male and female rats. Cystic keratinizing lesions that were diagnosed as squamous-cell carcinomas but re-evaluated as non-neoplastic pulmonary keratinizing cysts were also observed in the high-dose groups of female rats. Two inhalation studies in rats and one in female mice were negative.

Intratracheally instilled female rats showed an increased incidence of both benign and malignant lung tumours following treatment with two types of titanium dioxide. Tumour incidence was not increased in intratracheally instilled hamsters and female mice.

Oral, subcutaneous and intraperitoneal administration did not produce a significant increase in the frequency of any type of tumour in mice or rats.

5.4 Mechanistic considerations and other relevant data

Humans can be exposed to titanium dioxide via inhalation, ingestion or dermal contact. In human lungs, the clearance kinetics of titanium dioxide is poorly characterized relative to that in experimental animals. (General particle characteristics and host factors that are considered to affect deposition and retention patterns of inhaled, poorly soluble particles such as titanium dioxide are summarized in the monograph on carbon black.) With regard to

inhaled titanium dioxide, human data are mainly available from case reports that showed deposits of titanium dioxide in lung tissue as well as in lymph nodes. A single clinical study of oral ingestion of fine titanium dioxide showed particle size-dependent absorption by the gastrointestinal tract and large interindividual variations in blood levels of titanium dioxide. Studies on the application of sunscreens containing ultrafine titanium dioxide to healthy skin of human volunteers revealed that titanium dioxide particles only penetrate into the outermost layers of the stratum corneum, suggesting that healthy skin is an effective barrier to titanium dioxide. There are no studies on penetration of titanium dioxide in compromised skin.

Respiratory effects that have been observed among groups of titanium dioxide-exposed workers include decline in lung function, pleural disease with plaques and pleural thickening, and mild fibrotic changes. However, the workers in these studies were also exposed to asbestos and/or silica.

No data were available on genotoxic effects in titanium dioxide-exposed humans.

Many data on deposition, retention and clearance of titanium dioxide in experimental animals are available for the inhalation route. Titanium dioxide inhalation studies showed differences — both for normalized pulmonary burden (deposited mass per dry lung, mass per body weight) and clearance kinetics — among rodent species including rats of different size, age and strain. Clearance of titanium dioxide is also affected by pre-exposure to gaseous pollutants or co-exposure to cytotoxic aerosols. Differences in dose rate or clearance kinetics and the appearance of focal areas of high particle burden have been implicated in the higher toxic and inflammatory lung responses to intratracheally instilled *vs* inhaled titanium dioxide particles. Experimental studies with titanium dioxide have demonstrated that rodents experience dose-dependent impairment of alveolar macrophage-mediated clearance. Hamsters have the most efficient clearance of inhaled titanium dioxide. Ultrafine primary particles of titanium dioxide are more slowly cleared than their fine counterparts.

Titanium dioxide causes varying degrees of inflammation and associated pulmonary effects including lung epithelial cell injury, cholesterol granulomas and fibrosis. Rodents experience stronger pulmonary effects after exposure to ultrafine titanium dioxide particles compared with fine particles on a mass basis. These differences are related to lung burden in terms of particle surface area, and are considered to result from impaired phagocytosis and sequestration of ultrafine particles into the interstitium.

Fine titanium dioxide particles show minimal cytotoxicity to and inflammatory/pro-fibrotic mediator release from primary human alveolar macrophages *in vitro* compared with other particles. Ultrafine titanium dioxide particles inhibit phagocytosis of alveolar macrophages *in vitro* at mass dose concentrations at which this effect does not occur with fine titanium dioxide. In-vitro studies with fine and ultrafine titanium dioxide and purified DNA show induction of DNA damage that is suggestive of the generation of reactive oxygen species by both particle types. This effect is stronger for ultrafine than for fine titanium oxide, and is markedly enhanced by exposure to simulated sunlight/ultraviolet light.

In-vivo studies have shown enhanced micronucleus formation in bone marrow and peripheral blood lymphocytes of intraperitoneally instilled mice. Increased *Hprt* mutations were seen in lung epithelial cells isolated from titanium dioxide-instilled rats. In another study, no enhanced oxidative DNA damage was observed in lung tissues of rats that were

intratracheally instilled with titanium dioxide. The results of most in-vitro genotoxicity studies with titanium dioxide were negative.

6. Evaluation and rationale

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

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

Overall evaluation

Titanium dioxide is *possibly carcinogenic to humans (Group 2B)*.

Rationale

To follow

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