

Carcinogenicity Assessment of Titanium Dioxide

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Introduction

Titanium dioxide is a white mineral that is used to color paints, plastics, paper and other materials and is approved by the FDA as both a direct (with restricted uses) and indirect food additive. It is a non-genotoxic poorly soluble particulate. As such it has been found to not cause cancer by various routes in a number of animal models except for the rat. Titanium dioxide, as with other poorly soluble particulates, will cause lung tumors in rats when exposures are sufficient to cause particle overload, a condition associated with impaired particle clearance and macrophage function and chronic inflammation. The rat is particularly sensitive to developing this condition. This treatise discusses carcinogenic testing of titanium dioxide, mechanisms the development of lung tumors with particle overload, the uniqueness of the rat model and assessments of whether or not findings in the rat model indicate risk to man. Because there is a different potency in the rat model between pigmentary and ultrafine titanium dioxide, these are discussed separately.

Pigmentary Titanium Dioxide

Pigmentary titanium dioxide has particle sizes that range from 0.1-4 μm . It occurs naturally with a rutile or anatase crystalline structure and is made synthetically. It is used primarily as a pigment. Exposures have been found to cause lung tumors only in rats at exposures associated with persistent inflammation.

- **Cancer Testing**

Lung exposures to pigmentary titanium dioxide in rats are associated with adenomas and keratinized squamous cell tumors at exposures associated with chronic inflammation. Pigmentary titanium dioxide is not tumorigenic to the lungs in hamsters and is not tumorigenic with systemic exposures to rats or mice or orally to rats or mice. These studies are detailed as follows.

Lung Exposures

Trochimowicz et al (1988) completed a two year inhalation exposure study using pigmentary titanium dioxide at 10, 50 and 250 mg/m^3 . Evidence of inflammation (alveolar hyperplasia) was found at all exposure levels. In addition the two higher exposure levels bronchiolarization and minute collagen deposition associated with cholesterol giant cell granulomas developed. A tumorigenic effect was only found at 250 mg/m^3 . Tumors were microscopic, did not metastasize and only occurred after 24 months of exposure. Out of 151 exposed rats, 25 had bronchoalveolar adenomas and 14 keratinized squamous cell tumors, neither tumor type being found in man. Particle overload with persistent inflammation occurred at the two higher doses.

Thyssen et al (1978) exposed Sprague-Dawley rats to 15.95 mg/m³ of pigmentary titanium dioxide for 6 hr/d, 6 d/week for 12 weeks and then followed them for life. There was no significant difference in tumor incidence between exposed and control groups.

Intratracheal studies were done with pigmentary titanium dioxide in hamsters by Mohr et al (1984). No increases in tumor frequency were found at a dose of 8 mg when evaluated at 130 weeks. Stenback et al (1976) dosed hamsters with 3 mg of pigmentary titanium dioxide intratracheally each week for 15 weeks then observed them for 120 weeks. No increase in cancer frequency was found in the exposed group when compared to controls.

Borm et al (2000) dosed CPR/WU rats with six doses of 10 mg of pigmentary titanium dioxide. At 2 ½ years after exposure there was evidence of both alveolar (macrophage) and interstitial (polymorphonuclear cell (PMN)) inflammation. There was a 20.9% tumor frequency (27% microscopically) compared to 5-6% in controls. Tumor incidence was related linearly both to PMN and macrophage density. At the doses applied, saturation and retardation of macrophage clearance with particle overload was expected.

Systemic Exposures

Bischoff Bryson (1982) dosed Marsh Buffalo mice with 25 mg of pigmentary titanium dioxide intraperitoneally. No foreign body reaction and no increased tumor rate was seen over 18 months of observation.

Maltoni, et al (1982) treated Sprague-Dawley rats with 30 mg of 3 types of pigmentary titanium dioxide (including one coated with 10% silica) subcutaneously. No increased cancer frequency was noted when compared to controls.

Oral Studies

The National Toxicology Program (1979) conducted a lifetime feeding study of pigmentary titanium dioxide in Fischer 344 rats and B6C3F₁ mice with dosing to 5.0% in the diet. No cancer or other significant treatment-related effects were found. Bernard et al (1990) conducted a lifetime dietary study in Fischer 344 rats with 0, 0.1, 2.0 and 5.0% titanium dioxide-coated mica in diet. No toxicological or carcinogenic effects were seen.

- **Genotoxic Studies**

Genotoxic studies of titanium dioxide have been consistently negative. Titanium dioxide is not mutagenic to *Bacillus subtilis* (2 strains), is not active in the *B. subtilis* Rec – assay for DNA damage and does not enhance transformation of Syrian hamster embryo cells by SA virus (Bernard et al, 1990).

- **Epidemiological Studies**

Epidemiological studies involving exposures to pigmentary titanium dioxide have been negative. Frazer (2001) conducted a case-control study of bladder cancer. He found weak evidence of relationship between potential titanium dioxide exposure and bladder cancer with a relative risk of 1.5 that decreased to 1.3 (not significant) when he adjusted for potentially confounding variables.

Chen & Fayerweather (1988) studied titanium dioxide exposure among a cohort of 1576 exposed workers. The cohort analyses suggested that the risks of developing lung cancer and other fatal respiratory diseases were no higher for titanium dioxide-exposed employees than for the referent groups, with a relative risk of 0.52. A nested case-control analysis found no statistically significant associations between titanium dioxide exposure and risk of lung cancer.

Fayerweather et al (1992) further evaluated workers at two titanium dioxide production facilities. Cohort analyses showed that the risk of developing lung cancer and other fatal respiratory diseases was not statistically significantly higher for the titanium tetrachloride-exposed workers than for the referent group. With a multiple logistic regression analysis, the odds ratio for lung cancer death and exposure to titanium dioxide was 0.4 (95% CI 0.2-1.0).

Boffetta et al (2001) conducted a case control study of lung cancer in Montreal. They compared risk in workers exposed to titanium dioxide where exposures were considered low (0.5-1 mg/m³), medium (1-10 mg/m³) or high (11 mg to 400 mg/m³). The overall odds ratio for an exposure-effect relationship was 0.9 [95% confidence interval of 0.5-1.5]. No trend was apparent according to the estimated frequency, level, or duration of exposure.

Fryzek et al (2003) have reported on a cohort study of 4241 titanium dioxide-exposed workers. The relative risk for lung cancer was not significant at 1.0. No increases were found for any specific cause of death, including lung cancer. Mortality from lung cancer fell with increasing cumulative exposure, duration of exposure, or average exposure per year.

Clinical Studies

The effects of titanium dioxide has been evaluated in workers either from the analysis of sputum or lung specimens. The usual finding after years of exposure is a macrophage response with may or may not be associated with slight fibrosis. Polymorphonuclear cell inflammation, either in lung tissue or on lavage, is not described. Maatta & Arstila (1975) performed open lung biopsies in 3 workers after medical retirement from a titanium dioxide pigment factory. The authors found pigment aggregations in alveolar macrophages and extracellular areas accompanied by slight fibrosis. The also found pigment laden macrophages in sputum on bronchial lavage testing of 7 employees. Rode et al (1981) describe the autopsy of a man who had uncontrolled exposures to titanium dioxide. No inflammatory or fibrotic changes were described, only pigment deposition. Yamadori et al (1986) describe titanium dioxide-filled macrophages and slight pulmonary fibrosis in the autopsy of a worker who had packed titanium dioxide for 13 years.

- **Particle Reactivity**

Pigmentary titanium dioxide has a low level of surface reactivity compared to quartz, metal powders or ultrafine particles. Chronic inflammation has only been described under particle overload conditions in rats. Muhle et al (1989b) exposed Fischer 344 rats to 5 mg/m³ of pigmentary titanium dioxide for 6 hr/d, 5 d/ week for 2 years. Particle

accumulation was found but there was no epithelial reaction or fibrosis. In this same experiment, the authors evaluated bronchioloalveolar lavage (BAL) results in exposed and control rats (Muhle et al, 1991; Bellman et al, 1991). They found little evidence of inflammation with no increase in LDH, β -glucuronidase or protein in the BAL fluid. There was a slight increase in PMNs and a slight depression of alveolar clearance.

With higher exposures of pigmentary titanium dioxide to rats (22.5 mg/m³ 6 hr/d, 5 d/ wk for 3 months), Baggs et al (1997) found some fibrosis 6 months post exposure that was back to baseline 12 months post exposure. Janssen et al (1994) exposed rats to 22.3 mg/m³ of pigmentary titanium dioxide for 6 hr/d, 5 d/week for 12 weeks. This exposure failed to induce superoxide dismutase (MnSOD) formation. MnSOD removes active oxygen species and its induction is associated with inflammation. There was minimal evidence of inflammation or collagen deposition in this study.

Lee et al (1986) describe persistent inflammation at and exposure to pigmentary titanium dioxide of 50 mg/m³ for 6 hr/d, 5 d/week for 2 years. They found accumulation of foamy macrophages that were packed with phospholipids (surfactant derived from hyperplastic type II alveolar epithelial cells) but only a few particles, alveolar proteinosis and cholesterol granulomas. Abnormalities were first seen at 1 year from the start of exposure. Similar effects were seen at an exposure of 250 mg/m³ but the onset of inflammation was found at 6 months after initiating exposure. Bermudez et al (2002, 2003) confirmed these findings, exposing rats, mice and hamsters to pigmentary titanium dioxide from 10-250 mg/m³ for 13 weeks then observing them for an additional 52 weeks. Inflammation occurred in all 3 species at 50 and 250 mg/m³ but was more severe in rats. There was progressive epithelial and fibroproliferative changes at and exposure of 250 mg/m³ in rats with an increase in alveolar cell labeling (hyperplasia) and alveolar septal fibrosis. Warheit et al (1996b): found appreciable retention, cell proliferation and inflammation in rats exposed to 250 mg/m³ for 4 weeks. The authors felt that the effects (sustained proliferation and inflammation) were related to particle overload and not to the intrinsic activity of particles.

Schapira et al (1995) treated Fischer rats with 50 mg pigmentary titanium dioxide intratracheally, a level that would be expected to cause particle overload. Exposure caused inflammation with increases in LDH, protein, percent neutrophils and cells in BAL. However, there was no evidence of hydroxyl radical formation (an active oxygen species) using a salicylate hydroxylation product as a marker.

Ultrafine Titanium Dioxide

Ultrafine (UF) titanium dioxide is defined as synthetic, amorphous titanium dioxide with particle sizes that range from 20-50 nm. These particles agglomerate in air so that the mass median aerodynamic diameter exposures to UF titanium dioxide are similar to those of pigmentary titanium dioxide, ranging from 1-1.5 μ m. UF titanium dioxides are used as catalysts. Exposures occur to UF titanium dioxide smoke when welding with rutile-coated welding rods. As with pigmentary titanium dioxide, exposures to UF titanium dioxide have only been found to cause tumors in rats when inhaled at levels associated with particle overload and persistent inflammation.

- **Cancer Testing**

Lung Exposures

Heinrich et al (1995) exposed NMRI mice to 9.9 mg/m³ of UF titanium dioxide for 18 hr/d, 5 d/wk for 24 months. There was no lung tumor response. These authors similarly exposed Wistar rats and found a 32% tumor incidence (20% benign squamous cell tumors, 3% squamous carcinomas, 4% adenomas, and 13% adenocarcinomas) when analyzed at 30 months after the start of the experiment. Tumors were also found at the 18 and 24 month sacrifices in a similar frequency and distribution to that found at 30 months.

Rittenghausen et al (1997) exposed BR Wistar rats to 10.4 mg/m³ of UF titanium dioxide for 18 hr/d, 5 d/week for 24 months and followed them for an additional 6 months. They found 16% with cystic keratinizing epitheliomas, 3% with cystic keratinizing squamous cell carcinomas, and 1% with non-keratinizing squamous cell carcinomas.

Pott et al (1987) administered 100 mg of UF Titanium dioxide to Wistar rats by the intratracheal route. They found no lung cancers with this treatment. .

Borm et al (2000) treated CPR/WU rats with 30mg of UF titanium dioxide by the intratracheal route. At the time of sacrifice 2 ½ years later there was evidence of persistent alveolar (macrophage) and interstitial (PMN) inflammation. They found a 50% lung tumor rate. (66% microscopically) compared to 5-6% in controls. Tumor incidence related linearly both to the density of PMNs and macrophages in lung tissue. There was a lower level of inflammation than with pigmentary titanium dioxide administered in a similar fashion even though the tumor rate was higher. The authors felt that this finding could be explained by a greater degree of interstitialization of particles with the UF titanium dioxide exposures. At doses applied, saturation and retardation of macrophage clearance with particle overload would have been expected.

Systemic Exposures

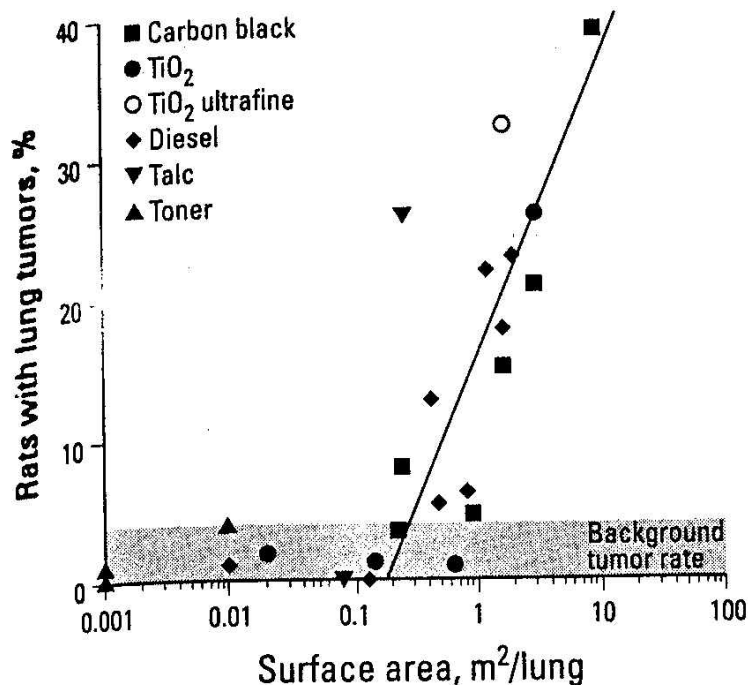
Pott et al (1987) treated Wistar rats with 5-10 mg of UF titanium dioxide intraperitoneally. They found no increased cancer rate compared to controls with this treatment.

- **Epidemiology**

Boffetta et al (2001) in a case-control study of lung cancer found no overall association between lung cancer and titanium dioxide exposure. In this study they found 5 cases exposed to UF titanium dioxide fumes vs. one referent (odds ratio 9.1, not significant). All of the cases had also been exposed to carcinogens by the inhalation route: 4 to chromium and nickel, 3 to benzo-a-pyrene and 2 to asbestos. Workers at some titanium dioxide production facilities will also be exposed to UF titanium dioxide. This was certainly true for the Chen & Fayerweather (1988) and Fayerweather et al (1992) studies where no excessive risk of lung cancer was identified. .

- **Particle Reactivity**

UF titanium dioxide causes considerably more inflammation with lung exposures than similar doses of pigmentary titanium dioxide. When exposures to insoluble, non-genotoxic particles, including pigmentary titanium dioxide and UF titanium dioxide, are compared, there is a linear relationship between retained dose, when expressed in turns of particle surface area per gm of lung tissue, and both risk of cancer and measures of inflammation, as noted in the following figure (Oberdorster, 1997):



The increased inflammatory and tumorigenic potential of UF particles is felt to be related to the increased surface area of these particles available to react with lung cell receptors. With low level exposure, inflammation either did not occur or was reversible. Particle overload does not occur in rats at exposures to UF titanium dioxide of 2 mg/m³ or less (Bermudez et al, 2003), equivalent to an exposure of 20 mg/m³ in humans (Yu, 1996).

Bermudez et al (2003) compared responses in rats to those in mice and hamsters exposed to UF titanium dioxide ranging from 0.5 to 10 mg/m³ for 13 weeks. They found no overload in hamsters. Overload in rats occurred at 1/5 the exposure necessary to cause overload in mice. Measures of inflammation were reversible in mice while there was progressive epithelial and fibroproliferative changes seen in rats exposed to 10 mg/m³ UF titanium dioxide but not at 2 mg/m³ or less.

Baggs et al (1997) and Janssen et al (1994) exposed rats to 23.5 mg/m³ of UF titanium dioxide for 6 hr/d, 5 d/wk for 6 months. They found more evidence of inflammation (rise in MnSOD and increases in enzymes in BAL) at 6 months post exposure than with

similar exposure level to pigmentary titanium dioxide. At 12 months post exposure, changes had reversed and fibrosis levels were no different from controls.

Gallagher et al (1994) exposed rats to 10.4 mg/m³ of UF titanium dioxide for 2 years. They found no DNA adduct formation even though there was a 32% incidence of lung tumors.

Dick et al (2003) treated rats with intratracheal UF titanium dioxide. They did not see the increase in PMNs, GGTP, or cytokines and depletion of supercoiled plasmid DNA (a measure of hydroxyl radical generation) at exposure levels which caused these changes with other UF metals, including cobalt and nickel, or with UF carbon black.

Nolan et al (1989): Evaluated 3 amorphous titanium dioxides and found that all were membranolytic on a human erythrocyte assay with the activity blocked by 2-PVPNO, an indication of elevated hydrogen binding activity. This was not seen with pigmentary Titanium dioxide samples.

Particle Overload

As with other non-genotoxic poorly soluble particles (such as coal and shale dusts), increased tumors found with over-exposures to titanium dioxide are associated with a overload conditions in exposed rats where a marked decrease in the ability to clear particles from the lungs is associated with severe, persistent inflammation and, at high exposures, tumor formation. The following is a summary of events associated with particle overload in rats.

“Particle overload is the consequence of exposure that results in a retained lung burden of particles that is greater than the steady-state burden predicted from the deposition rates and clearance kinetics of particles inhaled during exposure. The hallmark of particle overload is impaired alveolar clearance, which, in rats exposed to PSPs (poorly soluble particles), is associated with altered macrophage clearance function, pulmonary inflammation, centriacinar interstitial and alveolar accumulation of particles, and epithelial proliferation.” (ILSI, 2000). Increased incidence of lung tumors in rats exposed to PSPs is seen only seen under conditions of overload. Injurious reactive oxidants derived from inflammatory cells may cause genetic alterations that are fixed and propagated by increased epithelial proliferation. It was the consensus view of the ILSI workshop that “since the apparent responsiveness of the rat model at overload is dependent on coexistent chronic active inflammation and cell proliferation, at lower lung doses where chronic active inflammation and cell proliferation are not present, no lung cancer hazard is anticipated.”

Driscoll et al (1996) found a lack of association between the inherent genotoxic activity of low solubility particles and the development of rat lung tumors, implying a secondary mechanism for the response. When there is excessive exposure to titanium dioxide, there is an inflammatory response with associated release of chemokines. The latter are chemotactic and cause proliferation of type II alveolar epithelial cells.

Oberdorster et al (1994) and Driscoll et al (1993) found particle overload with UF titanium dioxide but not pigmentary titanium dioxide with similar exposures (22.3-23.5 mg/m³). With overload the interstitial burden of UF titanium dioxide particles accounted for >50% of the total lung burden 52 weeks after the last exposure. At 7 months post exposure there was continued inflammation (PMNs, protein, AMs in BAL), alveolar type II epithelial cell hyperplasia, and increased cytokine production (macrophage inflammatory proteins involved in chemotaxis).

Cullen et al (1999) found a threshold for decreased particle clearance in rats at a particle surface area loading of 200-300 cm² (equivalent to 3-30 mg/animal of UF titanium dioxide, depending on the particle surface area). When lung burdens were beyond 2000 cm², they noted persistent inflammation, even in absence of continued exposure, and associated tumors in rats. For low surface area loadings, macrophage migration/clearance is effective. When macrophages take up a large burden of particles, production of proinflammatory mediators (such as tumor necrosis factor), recruitment of neutrophils, and overload inflammation can occur. With overload inflammation, overproduction of phospholipids by type II epithelial cells occurs. Phagocytosis of this material results in marked impairment of macrophage mobility and ability to phagocytize with depressed particle clearance (Ferrin, 1982).

Lee et al (1986) noted that there was marked reduction in clearance when chronic inflammation occurred and that this was associated with appearance of foamy macrophages. These were found to disintegrate and release lysosomal enzymes and provoke cholesterol granulomas.

Driscoll et al (1990) found that rat alveolar macrophages that are “primed” by engulfing titanium dioxide particles release 200-400% greater levels of the cytokines tumor necrosis factor or interleukin-1 than control animals when exposed to lipopolysaccharide. This was seen with exposures to 10 mg/kg of pigmentary titanium dioxide, a level that gives marginal inflammation. These cytokines can facilitate inflammatory cell recruitment by activating endothelial cells and stimulate release of reactive oxygen species and lysosomes by macrophages and stimulate fibroblast proliferation.

Rat Model for Non-Genotoxic Aerosols

The rat is useful for determining the carcinogenic potential of genotoxic materials but may either be inappropriate or greatly exaggerate risks when evaluating exposures to non-genotoxic, poorly soluble particulates, including titanium dioxide.

There are certain pathological findings associated with particle overload from exposure to titanium dioxide and similar non-genotoxic particles that are unique to the rat including cholesterol granulomas and proliferative keratin cysts (Lee et al, 1986). These latter are felt by pathologists to be either a manifestation of metaplasia or benign tumors.

The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997) suggested that the rat lung tumors resulting from grossly overloading clearance mechanisms with particles may not be relevant to humans, and mentioned titanium

dioxide as an example. In monkeys and humans it appears that there is more interstitialization of deposited particles and less inflammation and epithelial cell proliferation than observed in the rat. In a 2 year inhalation study of poorly soluble particulates (PSPs) in monkeys at 2 mg/m^3 , there were inflammation or epithelial proliferation, though see those responses occurred in rats exposed to the same concentration. The greater sensitivity of rats to a neoplastic response may be related to a more proinflammatory environment with overwhelms oxidant defenses in the rat lung relative to other species. Rats exposed to PSPs exhibit a range of squamous cell proliferative responses that do not appear to have human analogies (ILSI, 2000).

Bermudez et al (2002) noted the primarily airspace aggregation of particles and particle laden macrophages in rats while particles are interstitial in humans and non-human primates. Mice also react differently than rats when exposed to poorly soluble particulates having less PMNs in BAL and none of the pathological changes.

Rittenghausen et al (1997) reported that the cystic keratinizing lesions seen in rat lungs after exposure in titanium dioxide were evaluated in a workshop of pathologists in Newark NJ in 1992. The majority agreed that the lesions should be considered as a non-neoplastic change, termed proliferative keratin cyst, while a minority of the pathologists considered the lesions as benign tumors. They considered these lesions have no significance to human health since comparable lesions have not been observed in humans. Valberg & Watson (1996) noted that transplanted cells from these proliferative keratin cysts failed to grow in nude (athymic) mice supporting the concept that these lesions are not neoplastic. The benign adenomas found in rats exposed to titanium dioxide and other PSPs also have no human counterpart.

The particle deposition and clearance dynamics in rats are such that they would exaggerate risk (markedly increase dose) when compared to man. Yu (1996) developed a deposition/clearance model for rats and compared the results to humans under the same exposure conditions. Rats were found to receive a dose rate in μg per gm of lung tissue in alveolar region 32 times that of humans. Clearance in humans, however, is 7.6 times less than that of rats. Over a 2 year exposure to 1 mg/m^3 of carbon black (an exposure not associated with particle overload), these differences resulted in a lung burden that was 10 times greater per gm for rats than humans. They further found that because of higher macrophage volume in humans (5 times greater than rats), and since particle overload appears to occur at high particle volumes in macrophages, that the reduction in clearance at high particle loading seen in rats would be less likely to occur at similar particle loadings in humans.

A major difference between rats and primates, including man, is the particle distribution after exposure to poorly soluble particles. Nikula et al (2001) found that rats retain particles in alveoli and alveolar ducts while identically exposed monkeys retain particles primarily in macrophages in the interstitium. While 81-85% of UF particles are seen in alveoli or alveolar ducts in exposed rats, in men exposed to coal dust at the $<2 \text{ mg/m}^3$ standard for average of 14.1 years, only 30% of particles are found in alveoli and alveolar ducts with the remainder in lymph nodes and interstitial tissues. This distribution would

promote alveolar/alveolar duct effects (hyperplasia and alveolitis) in rats and interstitial effects (fibrosis) in man under overexposure conditions.

Rats have a more inflammatory response to similar particle burdens of poorly soluble particles than other mammals, including man. This may be because of the rat's comparatively poor ability to handle oxidative stress, such as is seen with chronic lung inflammation. Carlsson et al (1996) found that rats produce superoxide dismutase in dimer form while most animals produce superoxide dismutase in tetramer form. The latter more effectively binds to tissues and may explain the finding of low tissue levels of superoxide dismutase in rats compared to man and other mammals. The production of superoxide dismutase occurs with lung tissue inflammation and this enzyme inactivates reactive oxygen species.

Assessments of Carcinogenicity

Both the International Agency for Research on Cancer (IARC) and the USEPA have made assessments on the carcinogenicity of titanium dioxide. IARC included in their evaluation an assessment of the inhalation study of Trochimowicz et al (1988). IARC's overall determination was that titanium dioxide is not classifiable as to its carcinogenicity in humans.

USEPA, as reported by Pepelko (1996), evaluated the carcinogenicity of titanium dioxide through a weight of evidence approach based upon number of positive studies, strength of the responses, possible confounding factors, and other evidence. They found that titanium dioxide exerts its harmful effects via particle overload. USEPA determined that risk of cancer was quite low and not quantitated. This conclusion was based on not finding detectable increases in carcinogenicity at exposure concentrations less than 250 mg/m³ for particles 2-3 μm diameter range, a level associated with severe overload conditions. Pepelko further noted that evidence is accumulating that the tumorigenic response for titanium dioxide are strongly influenced by lung particle overload. USEPA did not make a separate assessment of the carcinogenic potential of UF titanium dioxide.

Summary

Titanium dioxide, either in the pigmentary or ultrafine (UF) form, is considered a non-genotoxic poorly soluble particulate (PSP). As with other PSPs, exposure to titanium dioxide is not associated with a lung tumor risk at exposures below those that cause persistent lung inflammation. The latter occurs through a complex process associated with particle overload. In this process, particles activate lung cells in which they are engulfed to release cytokines and reactive oxygen species. This effect in turn results in the attraction of macrophages and polymorphonuclear cells (PMNs) with associated inflammation of the alveoli and alveolar ducts. When exposure is curtailed, inflammatory changes reverse and no lung tumors develop. In the rat when there are high level PSP exposures, this process can continue resulting in metaplastic change in these regions and the eventual formation of adenomas and proliferative keratin cysts. Neither of these lesions is found in man and the latter appears to be unique to the rat. Very high exposures of UF PSPs, including titanium dioxide, can result in the formation of adenocarcinomas and squamous cell carcinomas.

Because of differences in the deposition and clearance of particles in rat and man, when rat findings are extrapolated to man, exposures that result in particle loadings that cause particle overload in the rat are unlikely to occur in man. For instance, the human equivalent exposure to pigmentary titanium dioxide that is associated with adenomas and proliferative keratin cysts in rats would be 2500 mg/m³. The highest documented exposure to titanium dioxide in a titanium dioxide pigment production facility has been 400 mg/m³ with usual exposures <5 mg/m³. Particle overload occurs when there is an excessive macrophage particle burden. Because human macrophages are considerably larger than rat macrophages, it would be unlikely to have similar macrophage effects to those seen in the rat even if high deposition of titanium dioxide occurred. Clinical studies of heavily exposed workers confirm this assessment finding only macrophage and particle accumulation associated with slight fibrosis but no evidence of PMN inflammation, proliferation metaplasia or particle overload.

Particle overload associated with exposure to PSPs appears to be directly related to particle surface area. When comparing pigmentary to UF titanium dioxide, the latter appears to be approximately 5 fold more potent in causing lung overload, with a threshold for no effect at 2 mg/m³. When tumor incidences associated with exposures to UF titanium dioxide are compared to those of pigmentary titanium dioxide, and other PSPs, the increased tumor risk appears to be fully explained by particle surface area exposure.

Chronic exposure studies to titanium dioxide in experimental animals do not find an inflammatory or carcinogenic effect when exposure is by the systemic or oral route or to lungs in species other than rats. Rat studies find benign changes with pigmentary titanium dioxide exposures at sufficient levels to cause lung overload and chronic, persistent inflammation. Exposures to UF titanium dioxide in rats at sufficient levels to cause lung overload and chronic persistent inflammation result in metaplasia and tumors ranging from the benign to malignant.

Epidemiological studies of exposed workers have not found a significant increase in lung cancer risk (or cancer of other organs) even though such exposures were above the TLV for titanium dioxide (5 mg/m³). No increases in risk were noted with increasing cumulative exposure levels, average yearly exposure or duration of exposure. These workers would have been exposed to titanium dioxide both by inhalation and ingestion, the latter associated with particle clearance from the lungs via the mucociliary escalator system.

Assessments of the carcinogenic potential of titanium dioxide consider the risk associated with exposures to pigmentary titanium dioxide as being negligible to man and not quantitated by USEPA or IARC. When exposures are limited to prevent persistent inflammation, no risk of lung tumors would be expected. Current workplace exposure limits will prevent lung inflammation as documented by clinical studies of exposed workers.

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