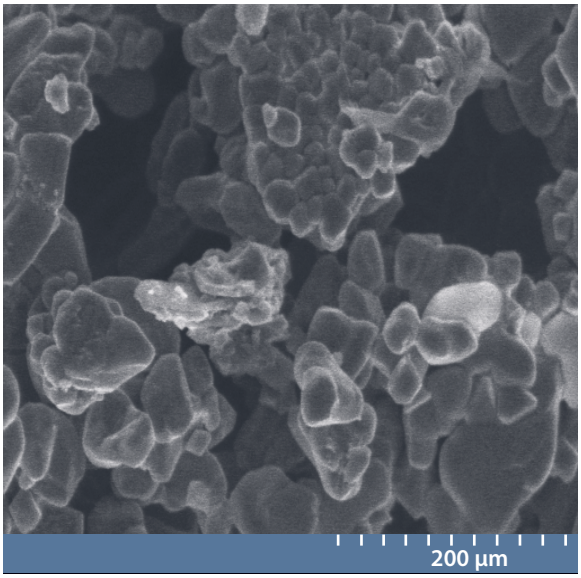
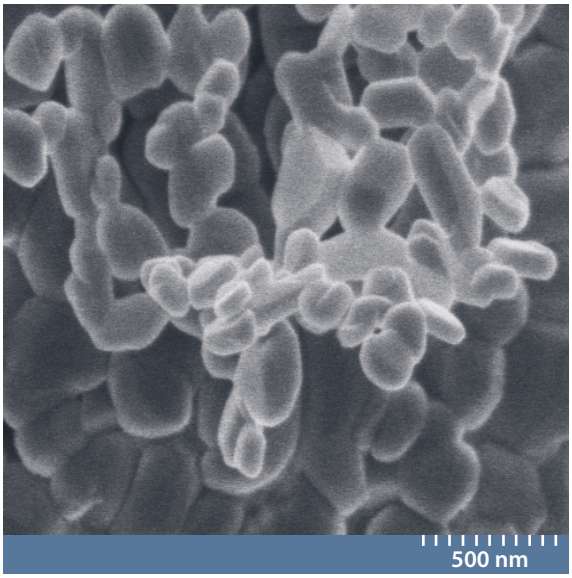
# CURRENT INTELLIGENCE BULLETIN 63

# Occupational Exposure to Titanium Dioxide




**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

On the cover left to right: (1) Scanning electron microscopy (SEM) image of agglomerated particles of pigment-grade rutile $TiO_2$; (2) SEM image of agglomerated ultrafine-sized particles of rutile $TiO_2$. Images courtesy of Bill Fox, Altairnano, Inc., and Dr. Aleks Stefaniak and Dr. Mark Hoover, NIOSH Nanotechnology Field Research Team. Used with permission.

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# Foreword

The purpose of the Occupational Safety and Health Act of 1970 (Public Law 91–596) is to assure safe and healthful working conditions for every working person and to preserve our human resources. In this Act, the National Institute for Occupational Safety and Health (NIOSH) is charged with recommending occupational safety and health standards and describing exposures that are safe for various periods of employment, including (but not limited to) the exposures at which no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience.

Current Intelligence Bulletins (CIBs) are issued by NIOSH to disseminate new scientific information about occupational hazards. A CIB may draw attention to a formerly unrecognized hazard, report new data on a known hazard, or disseminate information about hazard control. CIBs are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups as well as to federal agencies responsible for ensuring the safety and health of workers.

Titanium dioxide ($TiO_2$), an insoluble white powder, is used extensively in many commercial products, including paint, cosmetics, plastics, paper, and food, as an anticaking or whitening agent. It is produced and used in the workplace in varying particle-size fractions, including fine and ultrafine sizes. The number of U.S. workers currently exposed to $TiO_2$ dust is unknown.

This NIOSH CIB, based on our assessment of the current available scientific information about this widely used material, (1) reviews the animal and human data relevant to assessing the carcinogenicity and other adverse health effects of $TiO_2$, (2) provides a quantitative risk assessment using dose-response information from the rat and human lung dosimetry modeling and recommended occupational exposure limits for fine and ultrafine (including engineered nanoscale) $TiO_2$, and (3) describes exposure monitoring techniques, exposure control strategies, and research needs. This report only addresses occupational exposures by inhalation, and conclusions derived here should not be inferred to pertain to nonoccupational exposures.

NIOSH recommends exposure limits of 2.4 $mg/m^3$ for fine $TiO_2$ and 0.3 $mg/m^3$ for ultrafine (including engineered nanoscale) $TiO_2$, as time-weighted average (TWA) concentrations for up to 10 hours per day during a 40-hour work week. NIOSH has determined that ultrafine $TiO_2$ is a potential occupational carcinogen but that there are insufficient data at this time to classify fine $TiO_2$ as a potential occupational carcinogen. However, as a precautionary step, NIOSH used all of the animal tumor response data when conducting dose-response modeling and determining separate

RELs for ultrafine and fine $TiO_2$. These recommendations represent levels that over a working lifetime are estimated to reduce risks of lung cancer to below 1 in 1,000. NIOSH realizes that knowledge about the health effects of nanomaterials is an evolving area of science. Therefore, NIOSH intends to continue dialogue with the scientific community and will consider any comments about nano-size titanium dioxide for future updates of this document. (Send comments to nioshdocket@cdc.gov.)

NIOSH urges employers to disseminate this information to workers and customers and requests that professional and trade associations and labor organizations inform their members about the hazards of occupational exposure to respirable $TiO_2$.

John Howard, M.D.
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Centers for Disease Control and Prevention

# Executive Summary

In this Current Intelligence Bulletin, the National Institute for Occupational Safety and Health (NIOSH) reviews the animal and human data relevant to assessing the carcinogenicity of titanium dioxide ($TiO_2$) (Chapters 2 and 3), presents a quantitative risk assessment using dose-response data in rats for both cancer (lung tumors) and noncancer (pulmonary inflammation) responses and extrapolation to humans with lung dosimetry modeling (Chapter 4), provides recommended exposure limits (RELs) for fine and ultrafine (including engineered nanoscale) $TiO_2$ (Chapter 5), describes exposure monitoring techniques and exposure control strategies (Chapter 6), and discusses avenues of future research (Chapter 7). This report only addresses occupational exposures by inhalation, and conclusions derived here should not be inferred to pertain to nonoccupational exposures.

$TiO_2$ (Chemical Abstract Service [CAS] Number 13463–67–7) is a noncombustible, white, crystalline, solid, odorless powder. $TiO_2$ is used extensively in many commercial products, including paints and varnishes, cosmetics, plastics, paper, and food as an anticaking or whitening agent. Production in the United States was an estimated 1.45 million metric tons per year in 2007 [DOI 2008]. The number of U.S. workers currently exposed to $TiO_2$ dust is not available.

$TiO_2$ is produced and used in the workplace in varying particle size fractions including fine (which is defined in this document as all particle sizes collected by respirable particle sampling) and ultrafine (defined as the fraction of respirable particles with a primary particle diameter of <0.1 μm [<100 nm]). Particles <100 nm are also defined as nanoparticles.

The Occupational Safety and Health Administration (OSHA) permissible exposure limit for $TiO_2$ is 15 mg/m$^3$, based on the airborne mass fraction of total $TiO_2$ dust (Chapter 1). In 1988, NIOSH recommended that $TiO_2$ be classified as a potential occupational carcinogen and that exposures be controlled as low as feasible [NIOSH 2002]. This recommendation was based on the observation of lung tumors (nonmalignant) in a chronic inhalation study in rats at 250 mg/m$^3$ of fine $TiO_2$ [Lee et al. 1985, 1986a] (Chapter 3).

Later, a 2-year inhalation study showed a statistically significant increase in lung cancer in rats exposed to ultrafine $TiO_2$ at an average concentration of 10 mg/m$^3$ [Heinrich et al. 1995]. Two recent epidemiologic studies have not found a relationship between exposure to total or respirable $TiO_2$ and lung cancer [Fryzek et al. 2003; Boffetta et al. 2004], although an elevation in lung cancer mortality was ob-

served among male $TiO_2$ workers in the latter study when compared to the general population (standardized mortality ratio [SMR] 1.23; 95% confidence interval [CI] = 1.10–1.38) (Chapter 2). However, there was no indication of an exposure-response relationship in that study. Nonmalignant respiratory disease mortality was not increased significantly ($P$ <0.05) in any of the epidemiologic studies.

In 2006, the International Agency for Research on Cancer (IARC) reviewed $TiO_2$ and concluded that there was sufficient evidence of carcinogenicity in experimental animals and inadequate evidence of carcinogenicity in humans (Group 2B), "possibly carcinogenic to humans" [IARC 2010].

$TiO_2$ and other poorly soluble, low-toxicity (PSLT) particles of fine and ultrafine sizes show a consistent dose-response relationship for adverse pulmonary responses in rats, including persistent pulmonary inflammation and lung tumors, when dose is expressed as particle surface area. The higher mass-based potency of ultrafine $TiO_2$ compared to fine $TiO_2$ is associated with the greater surface area of ultrafine particles for a given mass. The NIOSH RELs for fine and ultrafine $TiO_2$ reflect this mass-based difference in potency (Chapter 5). NIOSH has reviewed and considered all of the relevant data related to respiratory effects of $TiO_2$. This includes results from animal inhalation studies and epidemiologic studies. NIOSH has concluded that $TiO_2$ is not a direct-acting carcinogen, but acts through a secondary genotoxicity mechanism that is not specific to $TiO_2$ but primarily related to particle size and surface area. The most relevant data for assessing the health risk to workers are results from a chronic animal inhalation study with ultrafine (<100 nm) $TiO_2$ in which a statistically significant increase in adenocarcinomas was observed [Heinrich et al. 1995]. This is supported by a pattern of $TiO_2$ induced responses that include persistent pulmonary inflammation in rats and mice [Everitt et al. 2000; Bermudez et al. 2004] and cancer responses for PSLT particles related to surface area. Therefore, on the basis of the study by Heinrich et al. [1995] and the pattern of pulmonary inflammatory responses, NIOSH has determined that exposure to ultrafine $TiO_2$ should be considered a potential occupational carcinogen.

For fine size (pigment grade) $TiO_2$ (>100 nm), the data on which to assess carcinogenicity are limited. Generally, the epidemiologic studies for fine $TiO_2$ are inconclusive because of inadequate statistical power to determine whether they replicate or refute the animal dose-response data. This is consistent for carcinogens of low potency. The only chronic animal inhalation study [Lee et al. 1985], which demonstrated the development of lung tumors (bronchioalveolar adenomas) in response to inhalation exposure of rats to fine sized $TiO_2$ did so at a dose of 250 mg/m$^3$ but not at 10 or 50 mg/m$^3$. The absence of lung tumor development for fine $TiO_2$ was also reported by Muhle et al. [1991] in rats exposed at 5 mg/m$^3$. However, the responses observed in animal studies exposed to ultrafine and fine $TiO_2$ are consistent with a continuum of biological response to $TiO_2$ that is based on particle surface area. In other words, all the rat tumor response data on inhalation of $TiO_2$ (ultrafine and fine) fit on the same dose-response curve when dose is expressed as total particle surface area in the lungs. However, exposure concentrations greater than 100

mg/m$^3$ are generally not considered acceptable inhalation toxicology practice today. Consequently, in a weight-of-evidence analysis, NIOSH questions the relevance of the 250 mg/m$^3$ dose for classifying exposure to $TiO_2$ as a carcinogenic hazard to workers and therefore, concludes that there are insufficient data at this time to classify fine $TiO_2$ as a potential occupational carcinogen. Although data are insufficient on the cancer hazard for fine $TiO_2$, the tumor-response data are consistent with that observed for ultrafine $TiO_2$ when converted to a particle surface area metric. Thus to be cautious, NIOSH used all of the animal tumor response data when conducting dose-response modeling and determining separate RELs for ultrafine and fine $TiO_2$.

NIOSH also considered the crystal structure as a modifying factor in $TiO_2$ carcinogenicity and inflammation. The evidence for crystal-dependent toxicity is from observed differences in reactive oxygen species (ROS) generated on the surface of $TiO_2$ of different crystal structures (e.g., anatase, rutile, or mixtures) in cell-free systems, with differences in cytotoxicity in *in vitro* studies [Kawahara et al. 2003; Kakinoki et al. 2004; Behnajady et al. 2008; Jiang et al. 2008, Sayes et al. 2006] and with greater inflammation and cell proliferation at early time points following intratracheal instillation in rats [Warheit et al. 2007]. However, when rats were exposed to $TiO_2$ in subchronic inhalation studies, no difference in pulmonary inflammation response to fine and ultrafine $TiO_2$ particles of different crystal structure (i.e., 99% rutile vs. 80% anatase/20% rutile) was observed once dose was adjusted for particle surface area [Bermudez et al. 2002, 2004]; nor was there a difference in the lung tumor response in the chronic inhalation studies in rats at a given surface area dose of these fine and ultrafine particles (i.e., 99% rutile vs. 80% anatase/20% rutile) [Lee et al. 1985; Heinrich et al. 1995]. Therefore, NIOSH concludes that the scientific evidence supports surface area as the critical metric for occupational inhalation exposure to $TiO_2$.

NIOSH also evaluated the potential for coatings to modify the toxicity of $TiO_2$, as many industrial processes apply coatings to $TiO_2$ particles. $TiO_2$ toxicity has been shown to increase after coating with various substances [Warheit et al. 2005]. However, the toxicity of $TiO_2$ has not been shown to be attenuated by application of coatings. NIOSH concluded that the $TiO_2$ risk assessment could be used as a reasonable floor for potential toxicity, with the notion that toxicity may be substantially increased by particle treatment and process modification. These findings are based on the studies in the scientific literature and may not apply to other formulations, surface coatings, or treatments of $TiO_2$ for which data were not available. An extensive review of the risks of coated $TiO_2$ particles is beyond the scope of this document.

NIOSH recommends airborne exposure limits of 2.4 mg/m$^3$ for fine $TiO_2$ and 0.3 mg/m$^3$ for ultrafine (including engineered nanoscale) $TiO_2$, as time-weighted average (TWA) concentrations for up to 10 hr/day during a 40-hour work week. These recommendations represent levels that over a working lifetime are estimated to reduce risks of lung cancer to below 1 in 1,000. The recommendations are based on using chronic inhalation studies in rats to predict lung tumor risks in humans.

In the hazard classification (Chapter 5), NIOSH concludes that the adverse effects of inhaling $TiO_2$ may not be material-specific but appear to be due to a generic effect of PSLT particles in the lungs at sufficiently high exposure. While NIOSH concludes that there is insufficient evidence to classify fine $TiO_2$ as a potential occupational carcinogen, NIOSH is concerned about the potential carcinogenicity of ultrafine and engineered nanoscale $TiO_2$ if workers are exposed at the current mass-based exposure limits for respirable or total mass fractions of $TiO_2$. NIOSH recommends controlling exposures as low as possible, below the RELs. Sampling recommendations based on current methodology are provided (Chapter 6).

Although sufficient data are available to assess the risks of occupational exposure to $TiO_2$, additional research questions have arisen. There is a need for exposure assessment for workplace exposure to ultrafine $TiO_2$ in facilities producing or using $TiO_2$. Other research needs include evaluation of the (1) exposure-response relationship of $TiO_2$ and other PSLT particles and human health effects, (2) fate of ultrafine particles in the lungs and the associated pulmonary responses, and (3) effectiveness of engineering controls for controlling exposures to fine and ultrafine $TiO_2$. (Research needs are discussed further in Chapter 7).

# Contents

# Abbreviations

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| BAL | bronchoalveolar lavage |
| BALF | bronchoalveolar lavage fluid |
| BAP | benzo(a)pyrene |
| $BaSO_4$ | barium sulfate |
| BET | Brunauer, Emmett, and Teller |
| BMD | benchmark dose |
| BMDL | benchmark dose lower bound |
| BMDS | benchmark dose software |
| °C | degree(s) Celsius |
| CAS | Chemical Abstract Service |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| cm | centimeter(s) |
| DNA | deoxyribonucleic acid |
| E | expected |
| EDS | energy dispersive spectroscopy |
| g | gram(s) |
| $g/cm^3$ | grams per cubic centimeter |
| g/ml | gram per milliliter |
| GSD | geometric standard deviation |
| *hprt* | hypoxanthine-guanine phosphoribosyl transferase |
| hr | hour(s) |
| IARC | International Agency for Research on Cancer |
| ICRP | International Commission on Radiological Protection |
| IR | incidence ratio |
| IT | intratracheal instillation |
| kg | kilogram |
| L | liter(s) |
| LCL | lower confidence limit |
| LDH | lactate dehydrogenase |
| m | meter(s) |
| MA | model average |

| | |
|---|---|
| MAK | Federal Republic of Germany maximum concentration value in the workplace |
| MCEF | mixed cellulose ester filter |
| mg | milligram(s) |
| mg/kg | milligram per kilogram body weight |
| $mg/m^3$ | milligrams per cubic meter |
| $mg/m^3 \bullet yr$ | milligrams per cubic meter times years |
| min | minute(s) |
| ml | milliliter(s) |
| ML | maximum likelihood |
| MLE | maximum likelihood estimate |
| mm | millimeter(s) |
| MMAD | mass median aerodynamic diameter |
| MPPD | multiple-path particle dosimetry |
| n | number |
| NAICS | North American Industry Classification System |
| NCI | National Cancer Institute |
| NIOSH | National Institute for Occupational Safety and Health |
| nm | nanometer(s) |
| NOAEL | no-observed-adverse-effect level |
| O | observed |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| *P* | probability |
| PBS | phosphate buffered saline |
| PEL | permissible exposure limit |
| PH | proportional hazards |
| PKT | pigmentary potassium titinate |
| PMN | polymorphonuclear leukocytes |
| PNOR/S | particles not otherwise regulated or specified |
| PNOR | particles not otherwise regulated |
| PNOS | particles not otherwise specified |
| PSLT | poorly soluble, low toxicity |
| REL | recommended exposure limit |
| ROS | reactive oxygen species |
| RNS | reactive nitrogen species |
| RR | relative risk |
| $SiO_2$ | silicon dioxide |
| SMR | standardized mortality ratio |
| TEM | transmission electron microscopy |

| | |
|---|---|
| $TiCl_4$ | titanium tetrachloride |
| $TiO_2$ | titanium dioxide |
| TWA | time-weighted average |
| UCL | upper confidence limit |
| U.K. | United Kingdom |
| UV | ultraviolet |
| U.S. | United States |
| wk | week(s) |
| µg | microgram(s) |
| µm | micrometer(s) |
| % | percent |

# Acknowledgments

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