DRAFT

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NIOSH CURRENT INTELLIGENCE BULLETIN:

Evaluation of Health Hazard and Recommendations for Occupational Exposure to Titanium Dioxide

EXECUTIVE SUMMARY

Titanium dioxide (TiO_2), an insoluble white powder, is used extensively in many commercial products, including paint, cosmetics, plastics, paper, and food as an anti-caking or whitening agent. Production in the United States was an estimated 1.43 million metric tons per year in 2004 [DOI 2005]. TiO_2 is a poorly soluble, low toxicity (PSLT) dust, which has been used as a negative control in experimental studies investigating particle toxicity. TiO_2 is produced and used in the workplace in varying particle size fractions including fine (approximately <2.5 μm diameter) and ultrafine (<0.1 μm diameter, primary particles, with larger agglomerates) [Aitken et al. 2004].

Current occupational exposure limits for TiO_2 are based on the airborne mass fractions of either respirable or total dust fractions. These exposure limits may be the same for TiO_2 and particles not otherwise regulated or classified (PNOR/C), with limits ranging from 1.5 mg/m^3 for respirable dust, the Federal Republic of Germany maximum concentration value in the workplace (MAK), to 15 mg/m^3 for total dust (Occupational Safety and Health Administration [OSHA]) (Chapter 1). NIOSH currently has no recommended exposure limit (REL) for TiO_2 and classifies it as a potential occupational carcinogen. 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).

In 1988, the International Agency for Research on Cancer (IARC) reviewed TiO_2 and concluded that there was limited evidence of carcinogenicity in experimental animals and inadequate evidence of carcinogenicity in humans (Group 3) [IARC 1989]. 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 observed 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 (i.e., $P < 0.05$) in any of the epidemiologic studies, although some studies may have lacked the statistical power to detect an effect.

The National Institute for Occupational Safety and Health (NIOSH) has reviewed the relevant animal and human data for assessing the carcinogenicity of TiO_2 and has reached the following conclusions. First, the tumorigenic effects of TiO_2 exposure in rats appear not to be chemical-specific or a direct action of the chemical substance itself. Rather, these effects appear to be a function of particle size and surface area acting through a secondary genotoxic mechanism associated with persistent inflammation. Second, current evidence indicates that occupational exposures to low concentrations of TiO_2 produce a negligible risk of lung cancer in workers.

On the basis of these findings, NIOSH has determined that insufficient evidence exists to designate TiO_2 as a "potential occupational carcinogen" at this time. NIOSH will reconsider this determination if further relevant evidence is obtained. However, evidence of tumorigenicity in rats at high exposure concentrations warrants the use of prudent health-protective measures for

workers until we have a more complete understanding of the possible health risks. Therefore, NIOSH recommends exposure limits for fine and ultrafine TiO_2 to minimize any risks that might be associated with the development of pulmonary inflammation and cancer.

In this document, NIOSH reviews the human, animal, and in vitro studies on TiO_2 (Chapters 2 and 3) and provides a quantitative risk assessment (Chapter 4), using dose-response data in rats for both cancer (lung tumors) and noncancer (pulmonary inflammation) responses and extrapolation to humans with lung dosimetry modeling. TiO_2 and other PSLT particles show a consistent dose-response relationship for 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 recommends exposure limits of 1.5 mg/m^3 for fine TiO_2 and 0.1 mg/m^3 for ultrafine TiO_2, as time-weighted average concentrations (TWA) for up to 10 hr/day during a 40-hour work week. These recommendations represent levels that over a working lifetime should reduce risks of lung cancer to below 1 in 1000. These exposure limits were established using the international definitions of respirable dust [CEN 1993; ISO 1995] and the NIOSH Method 0600 for sampling airborne respirable particles [NIOSH 1998].

"Respirable" is defined as particles of aerodynamic size that, when inhaled, are capable of depositing in the gas-exchange (alveolar) region of the lungs [ICRP 1994]. Sampling methods

have been developed to estimate the airborne mass concentration of respirable particles [CEN 1993; ISO 1995; NIOSH 1998]. "Fine" is defined in this document as all particle sizes that are collected by respirable particle sampling (i.e., 50% collection efficiency for particles of 4 μm, with some collection of particles up to10 μm) [CEN 1993; ISO 1995; NIOSH 1998]. "Ultrafine" is defined as the fraction of respirable particles with primary particle diameter <0.1 μm. Additional methods are needed to determine if an airborne respirable particle sample includes ultrafine TiO_2 (Chapter 6).

While the potential cancer potency of fine TiO_2 appears to be relatively low at current occupational exposures, NIOSH is concerned about the potential carcinogenicity of ultrafine 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 feasible below the RELs. Interim sampling recommendations based on current methodology are provided (Chapter 6).

A critical research need (discussed in Chapter 7) is measurement of workplace airborne exposures to ultrafine TiO_2 in facilities producing or using TiO_2. Other research needs include evaluation of the (1) exposure-response relationship between ultrafine PSLT particles and human health effects, (2) fate of ultrafine particles (e.g., TiO_2) in the lungs and the associated pulmonary responses, and (3) effectiveness of engineering controls for controlling exposures to fine and ultrafine TiO_2.

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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
BLS	U.S. Bureau of Labor Statistics
BMA	Bayesian model averaging
BMD	benchmark dose
BMDL	benchmark dose low
BMDS	benchmark dose software
°C	degree(s) Celsius
CAS	Chemical Abstract Service
CFR	Code of Federal Regulations
CI	confidence interval
CIIT	Centers for Health Research
cm	centimeter(s)
DNA	deoxyribonucleic acid
E	expected
EDXA	energy dispersive X-ray analyzer
EPA	U.S. Environmental Protection Agency
F	fine
g	gram(s)
g/cm^3	grams per cubic centimeter
g/ml	gram per milliliter
GSD	geometric standard deviation
HEPA	high efficiency particulate air
hprt	hypoxanthine-guanine phosphoribosyl transferase
hr	hour(s)
IARC	International Agency for Research on Cancer
ICP	inductively coupled argon plasma
ICRP	International Commission on Radiological Protection
Ig	immunoglobulin
IR	incidence ratio
kg	kilogram
L	liter(s)
LCL	lower confidence limit
LOD	limit of detection
m	meter(s)
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
$mg/m^3 \cdot yr$	milligrams per cubic meter times years

229	mg-yr/m^3	milligrams-years per cubic meter
230	min	minute(s)
231	ml	milliliter(s)
232	ML	maximum likelihood
233	MLE	maximum likelihood estimate
234	mm	millimeter(s)
235	MMAD	mass median aerodynamic diameter
236	MPPD	multi-path model of particle deposition
237	n	number
238	NCI	National Cancer Institute
239	NDICS	North American Industry Classification System
240	NIOSH	National Institute for Occupational Safety and Health
241	nm	nanometer(s)
242	NMRD	nonmalignant respiratory disease
243	NOES	National Occupational Exposure Survey
244	O	observed
245	OR	odds ratio
246	OSHA	Occupational Safety and Health Administration
247	*P*	probability
248	PEL	permissible exposure limit
249	PH	proportional hazards
250	PMN	polymorphonuclear leukocyte
251	PNOC	particles not otherwise classified
252	PNOC/R	particles not otherwise classified or regulated
253	PNOR	particles not otherwise regulated
254	PNOR/C	particles not otherwise regulated or classified
255	ppm	parts per million
256	PSLT	poorly soluble, low toxicity
257	PVC	polyvinyl chloride
258	REL	recommended exposure limit
259	RR	relative risk
260	RSD	relative standard deviation
261	SA	surface area
262	SIC	standard industrial classification
263	SiO_2	silicon dioxide
264	SIR	standardized incidence ratio
265	SMR	standardized mortality ratio
266	TEM	transmission electron microscopy
267	$TiCl_4$	titanium tetrachloride
268	TiO_2	titanium dioxide
269	TWA	time-weighted average
270	UCL	upper confidence limit
271	UF	ultrafine
272	U.K.	United Kingdom
273	UV	ultraviolet
274	U.S.	United States

wk	week(s)
µg	microgram(s)
µm	micrometer(s)
%	percent

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1. INTRODUCTION

1.1 COMPOSITION

Titanium dioxide (TiO_2) Chemical Abstract Service [CAS] (CAS Number 13463-67-7) is a noncombustible, white, crystalline, solid, odorless powder [NIOSH 2002; ACGIH 2001a]. TiO_2 is insoluble in water, hydrochloric acid, nitric acid, or alcohol, and it is soluble in hot concentrated sulfuric acid, hydrogen fluoride, or alkali [ACGIH 2001a]. TiO_2 has several naturally occurring mineral forms, or polymorphs, which have the same chemical formula and different crystalline structure. Common TiO_2 polymorphs include rutile (CAS Number 1317-80-2) and anatase (CAS Number 1317-70-0). While both rutile and anatase belong to the tetragonal crystal system, rutile has a denser arrangement of atoms (Figure 1-1).

At temperatures greater than 915 °C, anatase reverts to the rutile structure [http://mineral.galleries.com/minerals/oxides/anatase/anatase.htm]. The luster and hardness of anatase and rutile are also similar, but the cleavage differs. The density (specific gravity) of rutile is 4.25 g/ml [http://webmineral.com/data/Rutile.shtml], and that of anatase is 3.9 g/ml [http://webmineral.com/data/Anatase.shtml]. Common impurities in rutile include iron, tantalum, niobium, chromium, vanadium, and tin [http://www.mindat.org/min-3486.html], while those in anatase include iron, tin, vanadium, and niobium [http://www.mindat.org/min-213.html].

The sulfate process and the chloride process are two main industrial processes that produce TiO_2 pigment [IARC 1989; Boffetta et al. 2004]. In the sulfate process, anatase or rutile TiO_2 is produced by digesting ilmenite (iron titanate) or titanium slag with sulfuric acid. In the chloride process, natural or synthetic rutile is chlorinated at temperatures of 850 to 1000 °C [IARC 1989] and the titanium tetrachloride is converted to the rutile form by vapor-phase oxidation [Lewis

1993]. Both anatase and rutile are used as white pigment. Rutile TiO_2 is the most commonly used white pigment because of its high refractive index and relatively low absorption of light [Wicks 1993]. Anatase is used for specialized applications (e.g., in paper and fibers). TiO_2 does not absorb visible light, but it strongly absorbs ultraviolet (UV) radiation. Commercial rutile TiO_2 is prepared with an average particle size of 0.22 µm to 0.25 µm [Wicks 1993]. Pigment-grade TiO_2 refers to anatase and rutile pigments with a median particle size that usually ranges from 0.2 µm to 0.3 µm [Aitken et al. 2004]. Particle size is an important determinant of the properties of pigments and other final products [Wicks 1993].

1.2 USES

TiO_2 is used mainly in paints, varnishes, lacquer, paper, plastic, ceramics, rubber, and printing ink. TiO_2 is also used in welding rod coatings, floor coverings, catalysts, coated fabrics and textiles, cosmetics, food colorants, glassware, pharmaceuticals, roofing granules, rubber tire manufacturing, and in the production of electronic components and dental impressions [Lewis 1993; ACGIH 2001a; IARC 1989; DOI 2005]. Both the anatase and rutile forms of TiO_2 are semiconductors [Egerton 1997]. TiO_2 white pigment is widely used due to its high refractive index. Since the 1960s, TiO_2 has been coated with other materials (e.g., silica, alumina) for commercial applications [Lee et al. 1985].

1.3 PRODUCTION AND NUMBER OF WORKERS POTENTIALLY EXPOSED

An estimate of the number of workers currently exposed to TiO_2 dust is not available. The National Occupational Exposure Survey (NOES), conducted from 1981—1983, estimated that 2.7 million workers (2.2 million male, 0.5 million female) are potentially exposed to TiO_2 (CAS

Number 13463-67-7) in 42 standard industrial classifications (SICs) and 246 occupational groups [NIOSH 1983]. The SICs with the most workers potentially exposed include special trade contractors (0.36 million; SIC 17), machinery, except electrical (0.19 million; SIC 35), fabricated metal products (0.16 million; SIC 34), transportation equipment (0.16 million; SIC 37), and rubber and miscellaneous plastics products (0.15 million; SIC 30).

In 2004, an estimated 1.43 million metric tons of TiO_2 pigment were produced by four U.S. companies at eight facilities in seven states [DOI 2005]. The paint (includes varnishes and lacquers), plastic and rubber, and paper industries accounted for an estimated 95% of TiO_2 pigment used in the United States in 2004 [DOI 2005]. In 2003, the U.S. Bureau of Labor Statistics (BLS) estimated that there were about 70,000 U.S. workers in all occupations in paint, coating, and adhesive manufacturing (North American Industry Classification System [NAICS] code 325500), 829,000 in plastics and rubber products manufacturing (NAICS code 326000), and about 155,000 employed in pulp, paper, and paperboard mills [BLS 2003]. In 1991, TiO_2 was the 43rd highest-volume chemical produced in the United States [Lewis 1993].

1.4 CURRENT EXPOSURE LIMITS AND PARTICLE SIZE DEFINITIONS

Occupational exposure to TiO_2 is regulated by OSHA under the permissible exposure limit (PEL) of 15 mg/m^3 for TiO_2 as total dust (8-hr time-weighted average [TWA] concentration) [29 CFR* 1910.1000; Table Z-1]. The Occupational Safety and Health Administration (OSHA) PEL for particles not otherwise regulated (PNOR) is 5 mg/m^3 as respirable dust [29 CFR* 1910.1000; Table Z-1]. These and other exposure limits for TiO_2 and PNOR or PNOC (particles not

* See CFR in references.

otherwise classified) are listed in Table 1-1. PNOR/C are defined as all inert or nuisance dusts, whether mineral, inorganic or organic, not regulated specifically by substance name by OSHA (PNOR) or classified by ACGIH (PNOC). The same exposure limits are often given for TiO_2 and PNOR/PNOC (Table 1-1), and the Federal Republic of Germany maximum concentration value in the workplace (MAK) value for respirable TiO_2 specifically refers to the MAK general threshold value for dust [DFG 2000]. OSHA definitions for the total and respirable particle size fractions refer to specific sampling methods and devices [OSHA 2002], while the MAK and American Conference of Governmental Industrial Hygienists (ACGIH) definitions for respirable and inhalable are based on the internationally-developed definitions of particle size selection sampling [CEN 1993; ISO 1995; ACGIH 1984, 1994]. NIOSH also recommends the use of the international definitions [NIOSH 1995].

Aerodynamic diameter refers to how a particle behaves in air and determines the probability of deposition at locations within the respiratory tract. Aerodynamic diameter is defined as the diameter of a spherical particle that has the same settling velocity as a particle with a density of 1 g/cm^3 (the density of a water droplet) [Hinds 1999].

"Respirable" is defined as particles of aerodynamic size that, when inhaled, are capable of depositing in the gas-exchange (alveolar) region of the lungs [ICRP 1994]. Sampling methods have been developed to estimate the airborne mass concentration of respirable particles [CEN 1993; ISO 1995; ACGIH 1994; NIOSH 1998].

"Fine" is defined in this document as all particle sizes that are collected by respirable particle sampling (i.e., 50% collection efficiency for particles of 4 μm, with some collection of particles up to10 μm). "Fine" is also a common term that has been used in various ways. Fine is sometimes used to refer to the particle fraction between 0.1 μm and approximately 3 μm [Aitken et al 2004], and to refer to pigment-grade TiO_2 [e.g., Lee et al. 1985]. The term "fine" has been replaced by "respirable" by some organizations, e.g., MAK [DFG 2000], which is consistent with international sampling conventions [CEN 1993; ISO 1995].

"Ultrafine" is defined as the fraction of respirable particles with primary particle diameter <0.1 μm, which is a widely used definition. A primary particle is defined as the smallest identifiable subdivision of a particulate system [BSI 2005]. Additional methods are needed to determine if an airborne respirable particle sample includes ultrafine TiO_2 (Chapter 6). In this document, the terms fine and respirable are used interchangeably to retain both the common terminology and the international sampling convention.

In 1988, NIOSH classified TiO_2 as a potential occupational carcinogen and did not establish a recommended exposure limit (REL) for TiO_2 [NIOSH 2002]. This classification was based on the observation that TiO_2 caused lung tumors in rats in a long-term, high-dose bioassay [Lee et al. 1985]. NIOSH concluded that the results from this study met the criteria set forth in the OSHA cancer policy (29 CFR Part 1990, Identification, Classification, and Regulation of Carcinogens) by producing tumors in a long-term mammalian bioassay. The International Agency for Research on Cancer (IARC) classifies TiO_2 in Group 3, with limited evidence of

430 animal carcinogenicity and inadequate evidence for human carcinogenicity [IARC 1989]. The
431 scientific evidence pertaining to hazard classification and exposure limits for TiO_2 is reviewed
432 and evaluated in this document.
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Table 1-1. Occupational exposure limits and guidelines for TiO_2* and PNOS/R

Agency	TiO_2		PNOS/R	
	Single-shift TWA (mg/m^3)	Comments	Single-shift TWA (mg/m^3)	Comments
NIOSH [2002]†	—	Potential human carcinogen	—	—
OSHA	15	Total ‡	15 5	Total Respirable
ACGIH [2001a, 2001b, 2005]	10	Category A4 (not classifiable as a human carcinogen)	10§ 3§	Inhalable Respirable
MAK†† [DFG 2000]	1.5	Respirable	4 1.5	Inhalable Respirable

*Abbreviations: ACGIH = American Conference of Governmental Industrial Hygienists; MAK = Federal Republic of Germany Maximum Concentration Values in the Workplace; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PNOS/R = Particles not otherwise specified or regulated; TiO_2 = titanium dioxide; TWA = time-weighted average. TLV® = threshold limit value.

†Recommendations in effect before publication of this document.

‡*Total*, *inhalable*, and *respirable* refer to the particulate size fraction, as defined by the respective agencies.

§ PNOS guideline (too little evidence to assign TLV®). Applies to particles without applicable TLV, insoluble or poorly soluble, and low toxicity [ACGIH 2005]. Inorganic only; and for particulate matter containing no asbestos and <1% crystalline silica [ACGIH 2001b].

††MAK values are long-term averages. Single shift excursions are permitted within a factor of 2 of the MAK value.

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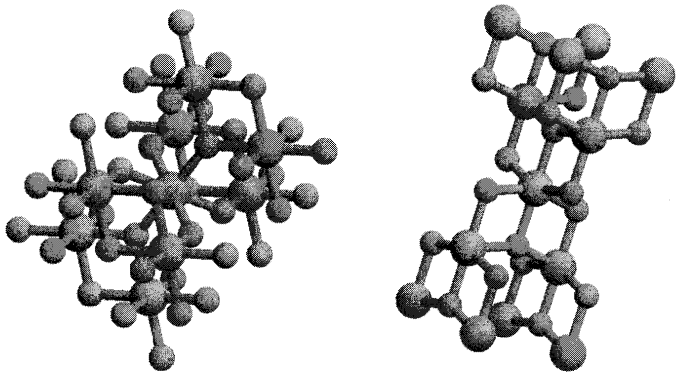

Rutile Anatase

Figure 1-1. Rutile and anatase TiO_2 crystal structure. (Courtesy: Cynthia Striley, NIOSH)

2. HUMAN STUDIES

2.1 CASE REPORTS

A few case reports described adverse health effects in workers with potential TiO_2 exposure. These effects included adenocarcinoma of the lung and TiO_2-associated pneumoconiosis in a male TiO_2 packer with 13 years of potential dust exposure and a 40-year history of smoking [Yamadori et al. 1986]. Pulmonary fibrosis or fibrotic changes and alveolar macrophage responses were identified by thoracotomy or autopsy tissue sampling in three workers with 6 to 9 years of dusty work in a TiO_2 factory. No workplace exposure data were reported. Two workers were "moderate" or "heavy" smokers (pack-years not reported) and smoking habits were not reported for the other worker [Elo et al. 1972]. Small amounts of silica were present in all three lung samples and significant nickel was present in the lung tissue of the autopsied case. Exposure was confirmed using sputum samples that contained macrophages with high concentrations of titanium two to three years after their last exposure [Määttä and Arstila 1975]. Titanium particles were identified in the lymph nodes of the autopsied case. The lung concentrations of titanium were higher than the lung concentration range of control autopsy specimens from patients not exposed to TiO_2 (statistical testing and number of controls not reported).

Moran et al. [1991] presented cases of TiO_2 exposure in four males and two females. However, occupation was unknown for one male and one female, and the lung tissue of one worker (artist/painter) was not examined (skin biopsy of arm lesions was performed). Smoking habits were not reported. Diffuse fibrosing interstitial pneumonia, bronchopneumonia, and alveolar metaplasia were reported in three male patients (a titanium dioxide worker, a painter, and a paper

mill worker) with lung-deposited TiO_2 (rutile) and smaller amounts of tissue-deposited silica [Moran et al. 1991]. Titanium was also identified in the liver, spleen, and one peribronchial lymph node of the TiO_2 worker, and talc was identified in the lungs of that patient and the paper mill worker.

A case of pulmonary alveolar proteinosis (i.e., deposition of proteinaceous and lipid material within the airspaces of the lung) was reported in a worker employed for more than 25 years as a painter, with 8 years of spray painting experience. He smoked two packs of cigarettes per day until he was hospitalized. Titanium was the major type of metallic particle found in his lung tissues [Keller et al. 1995].

Death occurred suddenly in a 26-year-old worker while pressure-cleaning inside a tank containing TiO_2; death was attributed to inhalation of the particulate [Litovitz et al. 2002; Litovitz 2004]. Further information about the role of TiO_2 was not provided.

In pathology studies of titanium dioxide workers, tissue-deposited titanium was often used to confirm exposure. In many cases, titanium rather than TiO_2, was identified in lung tissues; the presence of TiO_2 was inferred when a TiO_2-exposed worker had pulmonary deposition of titanium (e.g., Ophus et al. [1979]; Rode et al. [1981]; Määttä and Arstila [1975]; Elo et al. [1972]; Humble et al. [2003]). In other case reports, X-ray crystallography identified TiO_2 (i.e., anatase) in tissue digests [Moran et al. 1991] and X-ray diffraction distinguished rutile from anatase [Rode et al. 1981]. Similarly, with the exception of one individual in whom talc was identified [Moran et al. 1991], pathology studies (i.e., Elo et al. [1972]; Moran et al. [1991])

identified the silica as "SiO_2" (silicon dioxide) or "silica" in tissue and did not indicate whether it was crystalline or amorphous.

In summary, few TiO_2-related health effects were identified in case reports. None of the case reports provided quantitative industrial hygiene information about workers' TiO_2 dust exposure. Lung particle analyses indicated that workers exposed to respirable TiO_2 can accumulate particles in their lungs that may persist for years after cessation of exposure. TiO_2 deposited in the lungs of workers was often contaminated with other agents, most commonly silica (form not specified), at much lower concentrations than titanium particles. The chronic tissue reaction to lung-deposited titanium is distinct from chronic silicosis. Most cases of tissue-deposited titanium presented with a local macrophage response with associated fibrosis that was generally mild, but of variable severity, at the site of deposition. More severe reactions were observed in a few cases. The prevalence of similar histopathologic responses in other TiO_2-exposed populations is not known. The effects of concurrent or sequential exposure to carcinogenic particles, such as crystalline silica, nickel, and tobacco smoke, were not determined.

2.2 EPIDEMIOLOGIC STUDIES

A few epidemiologic studies have evaluated the carcinogenicity of TiO_2 in humans; they are described here and in Table 2-1. Epidemiologic studies of workers exposed to related compounds, such as titanium tetrachloride ($TiCl_4$) or titanium metal dust (i.e., Fayerweather et al. [1992] and Garabrant et al. [1987]) were not included because those compounds may have properties and effects that differ from those of TiO_2 and discussion of those differences is beyond the scope of this document.

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513 **2.2.1 Chen and Fayerweather [1988]**

514 Chen and Fayerweather [1988] conducted a mortality, morbidity, and nested case-control study
515 of 2,477 male wage-grade workers employed for more than 1 year before January 1, 1984 in two
516 TiO_2 production plants in the United States. The objectives of the study were to determine if
517 workers potentially exposed to TiO_2 had higher risks of lung cancer, chronic respiratory disease,
518 pleural thickening/plaques, or pulmonary fibrosis than referent groups.

519

520 Of the 2,477 male workers, 1,576 were potentially exposed to TiO_2. Other exposures included
521 $TiCl_4$, pigmentary potassium titinate (PKT), and asbestos. (The $TiCl_4$-exposed workers were
522 evaluated in Fayerweather et al. [1992]). Quantitative results from exposure monitoring or
523 sampling performed after 1975 may have been included in the study; however, it was unclear
524 what exposure measurements, if any, were available after 1975 and how they were used.
525 Committees (not described) were established at the plants to estimate TiO_2 exposures for all jobs.
526 A cumulative exposure index, duration, and TWA exposure were derived and used in the
527 analyses (details not provided).

528

529 Chest radiographic examination was used to detect fibrosis and pleural abnormalities and the
530 most recent chest X-ray of active employees (on 1/1/1984) was read blindly by two B-readers.

531

532 Observed numbers of cancer morbidity cases (i.e., incident cases) compared to expected numbers
533 were based on company rates. Observed numbers of deaths were compared to expected numbers
534 from company rates and national rates. Ninety percent (90%) acceptance ranges were calculated

for the expected numbers of cases or deaths. The nested case-control study investigated decedent lung cancer and chronic respiratory disease, incident lung cancer and chronic respiratory disease (not described), and radiographic chest abnormalities. Incidence data from the company's insurance registry were available from 1956 to 1985 for cancer and chronic respiratory disease. Mortality data from 1957 to 1983 were obtained from the company mortality registry. The study reported the number of observed deaths for the period 1935–1983; the source for deaths prior to 1957 is not clear.

Mortality from all cancers was lower than expected compared with U.S. mortality rates; however, mortality from all causes was greater than expected when compared with company rates (194 deaths observed; 175.5 expected; 90% acceptance range for the expected number of deaths=154-198). Lung cancer deaths were lower than expected based on national rates (9 deaths observed/17.3 expected=0.52; 90% acceptance range for the expected number of deaths=11–24) and company rates (9 deaths observed/15.3 deaths expected=0.59; 90% acceptance range for the expected number of deaths= 9–22). Lung cancer morbidity was not greater than expected (company rates; 8 cases observed; 7.7 expected; 90% acceptance range for the expected number of cases=3–13).

Nested case-control analyses found no association between TiO_2 exposure and lung cancer morbidity after adjusting for age, and exposure to $TiCl_4$, PKT, and asbestos (16 lung cancer cases; 898 controls; TiO_2 odds ratio [OR]=0.6). The OR did not increase with increasing average exposure, duration of exposure, or cumulative exposure index. No statistically significant positive relationships were found between TiO_2 exposure and cases of chronic respiratory

disease (88 cases; 898 noncancer, nonrespiratory disease controls; TiO_2 OR=0.8). Chest X-ray findings from 398 films showed few abnormalities—there were four subjects with "questionable nodules" but none with fibrosis. Pleural thickening or plaques were present in 5.6% (n=19) of the workers potentially exposed to TiO_2 compared with 4.8% (n=3) in the unexposed group. Case-control analyses of 22 cases and 372 controls with pleural abnormalities found a nonstatistically significant OR of 1.4 for those potentially exposed and no consistent exposure-response relationship.

Although this study did not report statistically significant increased mortality from lung cancer, chronic respiratory disease, or fibrosis associated with titanium exposure, serious limitations of the study precluded any conclusions: (1) it is unclear whether quantitative exposure data for respirable TiO_2 existed after 1975 and if so, whether those measurements were used in the analyses; (2) type of measurement (e.g., total, respirable, or submicrometer), type of sample (e.g., area or personal), number of samples, sampling location and times, and nature of samples (e.g., epidemiologic study or compliance survey), and breathing zone particle sizes were not reported; (3) duration of exposure was not described; (4) the presence of other chemicals and asbestos could have acted as confounders; (5) incidence and mortality data were not described in detail and could have been affected by the healthy worker effect; (6) chest X-ray films were not available for retired and terminated workers; and (7) company registries were the only apparent source for some information (e.g., company records may have been based on those workers eligible for pensions, and thus not typical of the general workforce.)

2.2.2 Fryzek et al. [2003]

Fryzek et al. [2003] conducted a retrospective cohort mortality study of 4,241 workers with potential exposure to TiO_2 employed on or after 1/1/1960 for at least 6 months at four TiO_2 production plants in the United States.

Plants used either a sulfate process or a chloride process to produce TiO_2 from the original ore. Nearly 2,400 records of air sampling measurements of sulfuric acid mist, sulfur dioxide, hydrogen sulfide, hydrogen chloride, chlorine, $TiCl_4$, and TiO_2 were obtained from the four plants. Most were area samples and many were of short duration. Full-shift or near full-shift personal samples (n=914; time-weighted averaging not reported) for total TiO_2 dust were used to estimate relative exposure concentrations between jobs over time. Total mean TiO_2 dust levels declined from 13.7 mg/m^3 in 1976–1980 to 3.1 mg/m^3 during 1996–2000. Packers, micronizers, and addbacks had about 3 to 6 times higher exposure concentrations than other jobs. Exposure categories, defined by plant, job title, and calendar years in the job, were created to examine mortality patterns in those jobs where the potential for TiO_2 exposure was greatest.

Mortality of 409 female workers and 3,832 male workers was followed until 12/31/2000 (average followup time=21 years; standard deviation=11 years). The number of expected deaths was based on mortality rates by sex, age, race, time period, and the state where the plant was located and standardized mortality ratios (SMRs) and confidence intervals (CIs) were calculated. Cox proportional hazards (PH) models that adjusted for effects of age, sex, geographic area, and date of hire were used to estimate relative risks (RR) of TiO_2 exposure (i.e., average intensity,

603 duration, and cumulative exposure) in medium or high exposure groups versus the lowest
604 exposure group.
605
606 Of the 4,241 workers (58% white; 90% male), 958 did not have adequate work history
607 information and were omitted from some plant analyses. Thirty-five percent of workers had been
608 employed in jobs with the highest potential for TiO_2 exposure. Workers experienced a
609 significantly low overall mortality (533 deaths; SMR=0.8; 95% CI=0.8-0.9). No significantly
610 increased SMRs were found for any specific cause of death, and there were no trends with
611 exposure. The number of deaths from trachea, bronchus, or lung cancer was not greater than
612 expected (i.e., 61 deaths; SMR=1.0; 95% CI=0.8-1.3), and SMRs for this cancer did not increase
613 with increasing TiO_2 concentrations. Workers in jobs with greatest TiO_2 exposure had
614 significantly fewer than expected total deaths (112 deaths; SMR=0.7; 95% CI=0.6-0.9) and
615 mortality from cancers of trachea, bronchus, or lung was not greater than expected (11 deaths;
616 SMR=1.0; 95% CI 0.5-1.7). Internal analyses (i.e., Cox PH models) revealed no significant
617 trends or exposure-response associations for total cancers, lung cancer, or other causes of death.
618 No association between TiO_2 exposure and increased risk of cancer death was observed in this
619 study (i.e., Fryzek et al. [2003]).
620
621 Limitations of this study include (1) company records from the early period were destroyed or
622 lost, (2) about half the cohort was born after 1940; lung cancer in these younger people would be
623 less frequent, and the latency from first exposure to TiO_2 short, (3) duration of employment was
624 often quite short, (4) no information about ultrafine exposures, and (5) limited data on
625 nonoccupational factors (e.g., smoking). Smoking information abstracted from medical records

from 1960 forward of 2,503 workers from the four plants showed no imbalance across job groups. In all job groups, the prevalence of smoking was about 55% and it declined over time by decade of hire. However, the information was inadequate for individual adjustments for smoking [Fryzek et al. 2003].

In addition, the RRs may have been artificially low, especially in the highest category of cumulative exposure, because of the statistical methods used [Beaumont et al. 2004]. Further data analyses by the authors found no significant exposure-response relationships for lung cancer mortality and cumulative TiO_2 exposure (i.e., "low", "medium", "high") with either a time-independent exposure variable or a time-dependent exposure variable and a 15-year exposure lag (adjusted for age, sex, geographic area, and date of hire) [Fryzek et al. 2004a,b]. However, the hazard ratio for trachea, bronchus, and lung cancer from "medium" cumulative TiO_2 exposure (15-year lag) was greater than 1.0 (hazard ratio for medium cumulative exposure, time-dependent exposure variable and 15-year lag=1.3; 95% CI 0.6-2.8) [Fryzek 2004a,b].

2.2.3 Boffetta et al. [2001]

Boffetta et al. [2001] reevaluated lung cancer risk from exposure to TiO_2 in a subset of a population-based case-control study of 293 substances including TiO_2 (i.e., Siemiatycki et al. [1991]; see Table 2-1 for description of Siemiatycki et al. [1991]).

Histologically confirmed lung cancer cases (n=857) from hospitals and noncancer referents were randomly selected from the population of Montreal, Canada. Cases were male, aged 35 to 70,

diagnosed from 1979 to 1985, and controls were 533 randomly selected healthy residents and 533 persons with cancer in other organs.

Job information was translated into a list of potential exposures, including all Ti compounds and TiO_2 as dust, mist, or fumes. Using professional judgment, industrial hygienists assigned qualitative exposure estimates to industry and job combinations worked by study subjects, based on information provided in interviews with subjects, proxies, and trained interviewers and recorded on a detailed questionnaire. The exposure assessment was conducted blindly (i.e., case or referent status not known). Duration, likelihood (possible, probable, definite), frequency (<5%, 5–30%, >30%), and extent (low, medium, high) of exposure were assessed. Those with probable or definite exposure for at least 5 years before the interview were classified as "exposed". Boffetta et al. [2001] classified exposure as "substantial" if it occurred for more than 5 years at a medium or high frequency and level. (Siemiatycki et al. [1991] used a different definition and included five workers exposed to titanium slag that were excluded by Boffetta et al. [2001]; see Table 2-1). Only 33 cases and 43 controls were classified as ever exposed to TiO_2 (OR= 0.9; 95% CI 0.5-1.5). Results of unconditional logistic models were adjusted for age, socioeconomic status, ethnicity, respondent status (i.e., self or proxy), tobacco smoking, asbestos, and benzo(a)pyrene (BAP) exposure. No trend was apparent for estimated frequency, level, or duration of exposure. The OR was 1.0 (95% CI= 0.3-2.7) for medium or high exposure for at least 5 years. Results did not depend on choice of referent group and no significant associations were found with TiO_2 exposure and histologic type of lung cancer.

The likelihood of finding a small increase in lung cancer risk was limited by the small number of cases assessed. However, the study did find an excess risk for lung cancer associated with both asbestos and BAP, indicating that the study was able to detect risks associated with potent carcinogens. The study had a power of 86% to detect an OR of 2 at the 5% level, and 65% power for an OR of 1.5.

Limitations of this study include (1) self-reporting or proxy reporting of exposure information, (2) use of surrogate indices for exposure, (3) absence of particle size characterization, and (4) the nonstatistically significant lung cancer OR for exposure to TiO_2 *fumes* was based on a small group of subjects and most were also exposed to nickel and chromium (5 cases; 1 referent; OR=9.1; 95% CI=0.7–118). In addition, exposures were limited mainly to those processes, jobs, and industries in the Montreal area. For example, the study probably included few, if any, workers that manufactured TiO_2. Most workers classified as TiO_2-exposed were painters and motor vehicle mechanics and repairers with painting experience; the highly exposed cases mixed raw materials for the manufacture of TiO_2-containing paints and plastics.

2.2.4 Boffetta et al. [2004]

Boffetta et al. [2004] conducted a retrospective cohort mortality study of lung cancer in 15,017 workers (14,331 men, 686 women) employed at least 1 month in 11 TiO_2 production facilities in six European countries. The factories produced mainly pigment-grade TiO_2. Estimated cumulative occupational exposure to respirable TiO_2 dust was derived from job title and work history. Observed numbers of deaths were compared with expected numbers based on national rates; exposure-response relationships within the cohort were evaluated using the Cox PH model.

Few deaths occurred in female workers (n=33); therefore, most analyses did not include female deaths. The followup period ranged from 1950–1972 until 1997–2001; 2,619 male and 33 female workers were reported as deceased. (The followup periods probably have a range of years because the followup procedures varied with the participating countries.) The cause of death was not known for 5.9% of deceased cohort members. Male lung cancer was the only cause of death with a statistically significant SMR (SMR=1.23; 95% CI= 1.10-1.38; 306.5 deaths (not a whole number because of correction factors for missing deaths). However, the Cox regression analysis of male lung cancer mortality found no evidence of increased risk with increasing cumulative respirable TiO_2 dust exposure (*P*-value for test of linear trend=0.5). There was no evidence of an exposure-response relationship for nonmalignant respiratory disease mortality. The authors suggested that lack of exposure-response relationships may have been related to a lack of (1) statistical power or (2) workers employed before the beginning of the followup period when exposure concentrations tended to be high. The authors also suggested that the statistically significant SMR for male lung cancer could represent (1) heterogeneity by country, (2) differences in the effects of potential confounders, such as smoking or occupational exposure to lung carcinogens, or (3) use of national reference rates instead of local rates.

2.3 SUMMARY OF EPIDEMIOLOGIC STUDIES

In general, the four epidemiologic studies of TiO_2-exposed workers represent a range of environments, from industry to population-based, and appear to be reasonably representative of worker exposures over several decades. One major deficiency is the absence of any cohort studies of workers who handle or use TiO_2 (rather than production workers).

716 Overall, these studies provide no clear evidence of elevated risks of lung cancer mortality or
717 morbidity among those workers exposed to TiO_2 dust.
718
719 Two of the three retrospective cohort mortality studies found small numbers of deaths from
720 respiratory diseases other than lung cancer and the number of pneumoconiosis deaths within that
721 category was not reported, indicating that these studies may have lacked the statistical power to
722 detect an increased risk of mortality from TiO_2-associated pneumoconiosis (i.e., Chen and
723 Fayerweather [1988]: 11 deaths from nonmalignant diseases of the respiratory system; Fryzek et
724 al. [2003]: 31 nonmalignant respiratory disease deaths).
725
726 In addition to the methodologic and epidemiologic limitations of the studies, they were not
727 designed to investigate the relationship between TiO_2 particle size and lung cancer risk, an
728 important question for assessing the potential occupational carcinogenicity of TiO_2.

Table 2-1. Summary of epidemiologic studies of workers exposed to TiO_2*

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure	95% CI	Adjusted for smoking	Comments
Boffetta et al. [2001], Canada	Population-based case-control study of 857 cases of histologically confirmed lung cancer diagnosed from 1979 to 1985 in men aged 35-70. Controls were randomly selected healthy residents (n=533) and persons with cancers of other organs (n=533).†	Ever exposed to TiO_2	33	OR=0.9	0.5–1.5	Yes	TiO_2 exposures were estimated by industrial hygienists based on occupational histories collected by Siemiatycki et al. [1991] and other sources. "Substantial" exposure defined as exposure for >5 years at a medium or high frequency and concentration. Lung cancer ORs were adjusted for age, family income, ethnicity, respondent (i.e., self or proxy), and smoking. Small number of cases ever exposed to TiO_2 (n=33). Limitations include self- or proxy-reporting of occupational exposures. Most TiO_2 fume-exposed cases (n=5) and controls (n=1) were also exposed to chromium and nickel.
		Substantial exposure to TiO_2	8	OR=1.0	0.3–2.7		
		Level of exposure:					
		Low	25	OR=0.9	0.5–1.7		
		Medium	6	OR=1.0	0.3–3.3		
		High	2	OR=0.3	0.07–1.9		
		Duration of exposure:					
		1-21 years	17	OR=1.0	0.5–2.0		
		≥ 22 years	16	OR=0.8	0.4–1.6		
		Exposed to TiO_2 fumes	5	OR=9.1	0.7–118		

See footnotes at end of table.

(Continued)

Table 2-1 (Continued). Summary of epidemiologic studies of workers exposed to TiO_2*

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure	95% CI	Adjusted for smoking	Comments
Boffetta et al. [2004], Finland, France, Germany, Italy, Norway, United Kingdom	Retrospective cohort mortality study of 15,017 workers (14,331 men) employed ≥ 1 month in 11 TiO_2 production facilities and followed for mortality from 1950-1972 until 1997-2001 (followup period varied by country). Employment records were complete from 1927-1969 until 1995-2001.	Male lung cancer: Cumulative respirable TiO_2 dust exposure ($mg/m^3 \cdot$ year): 0–0.73 0.73–3.43 3.44–13.19 13.20+ Male nonmalignant respiratory diseases: Cumulative respirable TiO_2 dust exposure ($mg/m^3 \cdot$ year): 0–0.8 0.9–3.8 3.9–16.1 16.2+	 53 53 52 53 40 39 40 39	 RR=1.00 RR=1.19 RR=1.03 RR=0.89 RR=1.00 RR=1.23 RR=0.91 RR=1.12	 Reference category 0.80–1.77 0.69–1.55 0.58–1.35 Reference category 0.76–1.99 0.56–1.49 0.67–1.86	Smoking data were available for 5,378 workers, but "since most available smoking data refer to recent years, no direct adjustment of risk estimates was attempted" [Boffetta et al. 2004].	No evidence of increased mortality risk with increasing cumulative TiO_2 dust exposure. (*P*-values for tests of linear trend were 0.5 and 0.6 for lung cancer mortality and nonmalignant respiratory disease mortality, respectively). Estimated cumulative TiO_2 dust exposure was derived from job title and work history. Exposure indices were not calculated when ›25% of the occupational history or ›5 years were missing. SMRs were not significantly increased for any cause of death except male lung cancer (SMR=1.23; 95% CI = 1.10-1.38; 306.5 deaths observed). Female workers were not included in most statistical analyses because of small number of deaths (n=33).

See footnotes at end of table.

(Continued)

Table 2-1 (Continued). Summary of epidemiologic studies of workers exposed to TiO_2[*]

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure	95% CI	Adjusted for smoking	Comments
Chen and Fayerweather [1988], United States	Mortality, morbidity, and nested case-control study of male, wage-grade employees of two TiO_2 production plants. Of 2,477 male employees, 1,576 were exposed to TiO_2. Study subjects worked >1 year before January 1, 1984. Mortality was followed from 1935 through 1983 and compared with U.S. white male mortality rates or company rates. Cancer and chronic respiratory disease incidence cases from 1956-1985 were available from company insurance registry. Case-control methods were applied to findings from 398 chest X-ray films from current male employees as of January 1, 1984.	Lung cancer deaths 1935-1983	9	O/E=0.52 (national rates)	11–24[‡]	Smoking histories were available for current workers; only use in X-ray case-control study was reported.	No statistically significant association or trends were reported. However, study has limitations (see text). Unclear source and exposure history of 898 controls in nested case-control study—may have been from company disease registry rather than entire worker population. Lung cancer OR was adjusted for age and exposure to $TiCl_4$, potassium titinate, and asbestos. "Chronic respiratory disease" was not defined. Controls (n=372) for pleural thickening case-control study were active employees with normal chest X-ray findings. ORs were adjusted for age, current cigarette smoking habits, and exposure to known respiratory hazards (not defined).
		Lung cancer deaths 1957-1983	9	O/E=0.59 (company rates)	9–22[‡]		
		Lung cancer cases 1956-1985	8	O/E=1.04 (company rates)	3–13[‡]		
		Lung cancer cases (case-control study)	16	OR=0.6	Not reported		
		Chronic respiratory disease cases (case-control study)	88	OR=0.8	Not reported		
		Pleural thickening/plaque cases (case-control study)	22	OR=1.4[§]	Not reported		

See footnotes at end of table.

(Continued)

Table 2-1 (Continued). Summary of epidemiologic studies of workers exposed to TiO_2*

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure	95% CI	Adjusted for smoking	Comments
Fryzek et al. [2003; 2004a,b], United States	Retrospective cohort mortality study of 409 female and 3,832 male workers employed ≥ 6 months on or after January 1, 1960, at four TiO_2 production facilities. The cohort was followed for mortality until the end of 2000. Mortality rates by sex, age, race, time period, and State where plant was located were used for numbers of expected deaths. Thirty-five percent (n=1,496) of workers were employed in jobs with high potential TiO_2 dust exposure (i.e., packers, micronizers, and addbacks).	Trachea, bronchus, lung cancer deaths	61	SMR=1.0	0.8–1.3	No	No statistically significant association was found for any cause of death. Models found no significant trends. Study limitations: (1) short followup period (avg. 21 years) and about half the cohort born after 1940; (2) more than half worked fewer than 10 years; (3) company records from early period lost or destroyed; (4) questionable modeling methods [Beaumont et al. 2004].
		High potential TiO_2 exposure	11	SMR=1.0	0.5–1.7		
		Nonmalignant respiratory disease deaths	31	SMR=0.8	0.6–1.2		
		High potential TiO_2 exposure	3	SMR=0.4	0.1–1.3		
		All causes of death	533	0.8	0.8–0.9		
		High potential TiO_2 exposure	112	0.7	0.6–0.9		
							914 full-shift or near full-shift personal air samples for TiO_2 dust were used in the analysis. Mean TiO_2 dust concentrations declined from 13.7 mg/m^3 ±17.9 (21 samples) in 1976-1980 to 3.1 mg/m^3 ± 6.1 (357 samples) in 1996-2000. They were 6.2 ± 9.4 mg/m^3 (686 samples) in jobs with high potential for TiO_2 exposure.

See footnotes at end of table.

(Continued)

Table 2-1 (Continued). Summary of epidemiologic studies of workers exposed to TiO_2*

Reference and country	Study design, cohort, and followup	Subgroup	Number of deaths or cases in subgroup	Risk measure	95% CI	Adjusted for smoking	Comments
Siemiatycki et al. [1991], Canada	Population-based case-control study of 3,730 histologically confirmed cases of 20 types of cancer diagnosed from September 1979 to June 1985 in men aged 35-70. 140 cases had some occupational TiO_2 exposure. There were two control groups: 533 population-based controls and a group of cancer patients.	Lung cancer cases with any occupational TiO_2 exposure	38	OR = 1.0	0.7–1.5**	Yes	Results provide little information about TiO_2-specific effects because this study evaluated 293 exposures, including TiO_2. Exposure was estimated by "chemist-hygienists" based on occupational histories. "Substantial" exposure defined as ›10 years in the industry or occupation up to 5 years before onset [Siemiatycki et al. 1991, p 122].
		Lung cancer cases with "substantial" occupational TiO_2 exposure	5	OR = 2.0	0.6–7.4**		
		Squamous cell lung cancer cases with any occupational TiO_2 exposure (population-based controls)	20	OR =1.6	0.9–3.0**		
		Squamous cell lung cancer cases with "substantial" occupational TiO_2 exposure	2	OR = 1.3	0.2–9.8**		
		Bladder cancer cases with any occupational TiO_2 exposure (cancer patient controls)	28	OR = 1.7	1.1–2.6**		
		Substantial occupational TiO_2 exposure	3	OR=4.5	0.9–22.0**		

*Abbreviations: CI = confidence Interval; O/E = observed number of deaths or cases divided by expected number of deaths or cases; OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; TiO_2 = titanium dioxide.
†Number of controls in Boffetta et al. [2001] subgroups: 43 ever exposed, 9 substantial exposure; 29 low exposure; 9 medium exposure; 5 high exposure; 22 worked 1-21 years; 21 worked ≥ 22 years.
‡90% acceptance range for the expected number of deaths or cases
§Reported as "not statistically significantly elevated."
**90% CI.

729

3. EXPERIMENTAL STUDIES IN ANIMALS AND COMPARISON TO HUMANS

3.1 IN VITRO STUDIES

3.1.1 Genotoxicity and Mutagenicity

TiO_2 (particle size not specified) did not show genotoxic activity in several standard assays: cell-killing in deoxyribonucleic acid (DNA)-repair deficient *Bacillus subtilis*; mutagenesis in *Salmonella typhimurium* or *E. coli*; or transformation of Syrian hamster embryo cells [IARC 1989]. However, more recent studies have shown that TiO_2 can induce micronuclei in Chinese hamster ovary cells, particularly when a cytokinesis-block technique is employed; TiO_2 can also induce sister chromatid exchanges [Lu et al. 1998]. In addition, ultrafine TiO_2 (approx. 20 nm particle size) can induce apoptosis in Syrian hamster embryo cells [Rahman et al. 2002]. TiO_2 has demonstrated genotoxic activity following photoactivation [Nakagawa et al. 1997], which may have some relevance to dermal exposures. Overall, these studies suggest that TiO_2 may have some genotoxic potential, under some conditions.

3.1.2 Effects on Phagocytosis

Renwick et al. [2001] reported that both fine and ultrafine TiO_2 particles (250 and 29 nm mean diameter, respectively) reduced the ability of J774.2 mouse macrophages to phagocytose 2 μm latex beads, in vitro. Ultrafine TiO_2 impaired macrophage phagocytosis at a lower mass dose than fine TiO_2. Möller et al. [2002] found that ultrafine TiO_2 (20 nm diameter), but not fine TiO_2 (220 nm diameter), caused impaired phagosomal transport and increased cytoskeletal stiffness in both J774A.1 mouse macrophages and alveolar macrophages isolated from beagle dogs.

753 However, this study was not able to replicate the Renwick et al. [2001] finding that phagocytosis
754 was more strongly inhibited by ultrafine TiO_2 than by fine TiO_2. The reason for this discrepancy
755 is unknown.
756
757 **3.2 SUBCHRONIC STUDIES**
758 **3.2.1 Intratracheal Instillation**
759 Studies with male Fischer 344 rats instilled with 0.5 mg of TiO_2 of four different particle sizes
760 (12 to 250 nm) indicate that ultrafine TiO_2 particles are interstitialized to a greater extent and
761 cleared from the lung more slowly than larger TiO_2 particles [Ferin et al. 1992]. Other
762 intratracheal instillation studies conducted by the same laboratory suggest that ultrafine TiO_2
763 particles produce a greater acute (24-hr) pulmonary inflammation response than larger TiO_2
764 particles, and that the increased toxicity of the ultrafine particles appears to be related to their
765 surface area and to their increased interstitialization [Oberdörster et al. 1992].
766
767 Rehn et al. [2003] also observed an acute (3-day) inflammatory response to instillation of
768 ultrafine TiO_2 and found that the response from a single instillation decreased over time,
769 returning to control levels by 90 days after the instillation. The reversibility of the inflammatory
770 response to ultrafine TiO_2 contrasted with the progressive increase in inflammation over 90 days
771 that was seen with crystalline silica (quartz) in the same study. This study also compared a
772 silanized hydrophobic preparation of ultrafine TiO_2 to an untreated hydrophilic form, and
773 concluded that alteration of surface properties by silanization does not greatly alter the biological
774 response of the lung to ultrafine TiO_2.
775

In another study, type II alveolar cells were isolated, 15 months after dosing, from rats dosed by intratracheal instillation with either 10 or 100 mg/kg of fine TiO_2 [Driscoll et al. 1997]. Type II cells isolated from rats dosed with 100 mg/kg fine TiO_2 exhibited an increased hypoxanthine-guanine phosphoribosyl transferase (*hprt*) mutation frequency, but type II cells isolated from rats treated with 10 mg/kg fine TiO_2 did not. Neutrophil counts were significantly elevated in the bronchoalveolar lavage fluid (BALF) isolated from rats instilled 15 months earlier with 100 mg/kg fine TiO_2, as well as by 10 or 100 mg/kg of α-quartz or carbon black. *Hprt* mutations could be induced in RLE-6TN cells in vitro by cells from the BALF isolated from the 100 mg/kg fine TiO_2-treated rats. The authors concluded that the results supported a role for particle-elicited macrophages and neutrophils in the in vivo mutagenic effects of particle exposure, possibly mediated by cell-derived oxidants.

Mice instilled with 1 mg fine TiO_2 showed no evidence of inflammation at 4, 24, or 72 hr after instillation as assessed by inflammatory cells in bronchoalveolar lavage (BAL) and expression of a variety of inflammatory cytokines in lung tissue [Hubbard et al. 2002].

An intratracheal instillation study in hamsters suggested that fine TiO_2 may act as a co-carcinogen [Stenbäck et al. 1976]. When BAP and fine TiO_2 were administered intratracheally to 48 hamsters, 16 laryngeal, 18 tracheal, and 18 lung tumors developed, compared to only 2 laryngeal tumors found in the BAP-treated controls.

3.2.2 Short-Term Inhalation

Short-term exposure to respirable fine TiO_2 resulted in particle accumulation in the lungs of exposed rats. The pulmonary retention of these particles increased as exposure concentrations increased. Thus, after 4 weeks of exposure to 5 mg/m^3, 50 mg/m^3, and 250 mg/m^3, the fine TiO_2 retention half-life in the lung was ~68 days, ~110 days, and ~330 days, respectively [Warheit et al. 1997], which is indicative of lung clearance overload.

In multiple studies, the most frequently noted change after 1 to 4 weeks of fine TiO_2 inhalation was the appearance of macrophages laden with particles, which were principally localized to the alveoli, bronchus-associated lymphoid tissue, and lung-associated lymph nodes [Driscoll et al. 1991; Warheit et al. 1997; Huang et al. 2001]. Particle-laden macrophages increased in number with increasing exposure intensity and decreased in number after cessation of exposure [Warheit et al. 1997]. Alveolar macrophages from rats inhaling 250 mg/m^3 fine TiO_2 for 4 weeks also appeared to be functionally impaired as demonstrated by persistently diminished chemotactic and phagocytic capacity [Warheit et al. 1997].

Inflammation in the lungs of fine TiO_2-exposed rats was dependent upon exposure concentration and duration. Rats exposed to 250 mg/m^3 fine TiO_2 6 hr/day, 5 days/week for 4 weeks had markedly increased numbers of granulocytes in BALF [Warheit et al. 1997]. The granulocytic response was muted after recovery, but numbers did not approach control values until 6 months after exposures ceased. Rats exposed to 50 mg/m^3 fine TiO_2 6 hr/day, 5 days/wk for 4 weeks had a small but significantly increased number of granulocytes in the bronchoalveolar fluid that returned to control levels at 3 months after exposures ceased [Warheit et al. 1997].

Another study reported that the inflammatory lesions in Fischer 344 rats produced by 3-month exposures to either 22.3 mg/m^3 of ultrafine TiO_2, or 23.5 mg/m^3 of pigment-grade TiO_2 "regressed during a 1-year period following cessation of exposure" [Baggs et al. 1997]. This observation suggests that the inflammatory response from short-term exposures to TiO_2 may be reversible to some degree, if there is a cessation of exposure.

In a separate study, rats exposed to inhalation concentrations of 50 mg/m^3 fine TiO_2 7 hr/day, 5 days/week for 75 days had significantly elevated neutrophil numbers, lactate dehydrogenase (a measure of cell injury) concentration, and *n*-acetylglucosaminidase (a measure of inflammation) concentration in BALF [Donaldson et al. 1990]. However, in that study the BALF of rats inhaling 10 mg/m^3 or 50 mg/m^3 fine TiO_2, 7 hr/day, 5 days/week for 2 to 52 days had polymorphonuclear leukocyte numbers, macrophage numbers, and lactate dehydrogenase concentrations that were indistinguishable from control values [Donaldson et al. 1990].

Rats exposed to airborne concentrations of 50 mg/m^3 fine TiO_2 6 hr/day for 5 days had no significant changes in BALF neutrophil number, macrophage number, lymphocyte number, lactate dehydrogenase concentration, *n*-acetylglucosaminidase concentration, or measures of macrophage activation 1 to 9 weeks after exposure [Driscoll et al. 1991]. Similarly, rats exposed to 0.1, 1, or 10 mg/m^3, 6 h/day, 5 days/week for 4 weeks or intratracheally instilled with up to 750 μg TiO_2 had no evidence of lung injury as assessed by BAL 1 week to 6 months after exposure or histopathology at 6 months after exposure [Henderson et al. 1995].

Rats exposed to very high concentrations (1130-1310 mg/m^3) of 6 different formulations of fine TiO_2 for 30 days (6 hr/day, 5 days/week), or intratracheally instilled with 2 or 10 mg/kg of the same formulations, showed varying degrees of pulmonary inflammation, depending on the surface coating applied to the TiO_2. The greatest inflammatory responses were induced by TiO_2 coated with both alumina and amorphous silica [Warheit et al. 2005].

3.2.3 Subchronic Inhalation

Several studies have investigated the rat lung responses, including pulmonary inflammation, to subchronic inhalation (up to 6 months) of fine and ultrafine TiO_2 [Oberdörster et al. 1994, 1992; Ferin et al. 1992], other low toxicity dust (barium sulfate [$BaSO_4$]) [Tran et al. 1999] or high toxicity dust (crystalline silica, SiO_2) [Porter et al. 2001]. Figures 3-1 and 3-2 show the relationship between particle dose (as mass or surface area) of these various particles and pulmonary inflammation. When particle lung dose is expressed as mass, the data fall on different dose-response curves for the different particles (Figure 3-1). However, when dose is converted to particle surface area (Figure 3-2), both of the poorly soluble, low toxicity (PSLT) particles fit the same dose-response curve, with crystalline silica (considered a higher-toxicity particle) demonstrating more inflammogenic response when compared to PSLT particles of a given surface area dose.

Subchronic (13-week) inhalation exposure of rats, mice and hamsters to 10, 50, or 250 mg/m^3 concentrations of fine TiO_2 resulted in alveolar epithelial changes, cell damage and inflammation at high exposure concentrations in all three species [Everitt et al. 2000; Bermudez et al. 2002].

Inhaling 50 or 250 mg/m^3 fine TiO_2 for 13 weeks caused histopathologic changes consistent with alveolar epithelial cell hypertrophy and hyperplasia in all species [Everitt et al. 2000]. Foci of alveolar epithelial cell hypertrophy and hyperplasia were often associated with aggregates of particle-laden alveolar macrophages in rats, mice, and hamsters [Bermudez et al. 2002]. In rats, but not mice and hamsters, these foci of alveolar epithelial hypertrophy became increasingly more prominent with time, even after cessation of exposure, and in high dose rats progressed to bronchiolization of alveoli (metaplasia) and fibrotic changes with focal interstitialization of TiO_2 particles [Bermudez et al. 2002]. Alveolar lipoproteinosis and cholesterol clefts were also observed in subchronically exposed rats after cessation of exposure [Bermudez et al. 2002]. In addition, in rats, alveolar cell turnover was increased in alveoli not associated with inflammatory foci [Bermudez et al. 2002]. In the BALF of rats, mice and hamsters exposed to 250 mg/m^3 fine TiO_2 the numbers of macrophages, the percentage of neutrophils in BALF, lactate dehydrogenase (a measure of cell damage) and total protein significantly increased. While these changes were reversible in hamsters by 13 to 26 weeks after exposure cessation, they persisted in rats and mice through 52 weeks after cessation of the 250 mg/m^3 exposure. These effects also persisted in rats and mice inhaling 50 mg/m^3 fine TiO_2 for at least 13 weeks after exposure cessation [Bermudez et al. 2002].

3.3 CHRONIC STUDIES

3.3.1 Rat Lung Tumor Response

TiO_2 has been investigated in three chronic inhalation studies in rats, including fine TiO_2 in Lee et al. [1985] and Muhle et al. [1991] and ultrafine TiO_2 in Heinrich et al. [1995]. These studies were also reported in other publications, including Lee et al. [1986a], Muhle et al. [1989, 1994],

and Bellmann et al. [1991]. In another 2-year rat inhalation study, an increase in lung carcinomas was found in rats exposed to titanium tetrachloride [Lee et al. 1986b]; however, titanium tetrachloride is a different compound with different properties than TiO_2, and will not be discussed further in this document.

In Lee et al. [1985], groups of 100 male and 100 female rats (CD, Sprague-Dawley derived; strain not specified) were exposed by whole body inhalation to fine, rutile TiO_2 (pigment grade) for 6 hr/day, 5 days/week, for 2 years, to 10, 50, or 250 mg/m^3 (84% respirable). A fourth group (control) was exposed to air. The particle size of the TiO_2 was 1.5 to 1.7 μm mass median aerodynamic diameter (MMAD) diameter. No increase in lung tumors was observed at 10 or 50 mg/m^3. At 250 mg/m^3, bronchioalveolar adenomas were observed in 12/77 male rats and 13/74 female rats. In addition, squamous cell carcinomas were reported in 1 male and 13 females at 250 mg/m^3. The squamous cell carcinomas were noted as being dermoid, cyst-like squamous cell carcinomas [Lee et al. 1985], and were later reclassified as proliferative keratin cysts [Carlton 1994], and later still as a continuum ranging from pulmonary keratinizing cysts through pulmonary keratinizing eptheliomas to frank pulmonary squamous carcinomas [Boorman et al. 1996].

In both the Muhle et al. [1991] and Heinrich et al. [1995] studies, TiO_2 was used as a negative control in 2-year chronic inhalation studies of toner and diesel exhaust, respectively. In Muhle et al. [1991], the airborne concentration of TiO_2 (rutile) was 5 mg/m^3 (77% respirable). Male and female Fischer 344 rats were exposed for up to 24 months by whole body inhalation, and sacrificed beginning at 25.5 months. No increase in lung tumors was observed in TiO_2-exposed

animals; the lung tumor incidence was 2/100 in TiO_2-exposed animals versus 3/100 in nonexposed controls.

In the Heinrich et al. [1995] study, 100 female Wistar rats were exposed to ultrafine TiO_2 (anatase) at an average of approximately 10 mg/m^3 for 2 years (actual concentrations were 7.2 mg/m^3 for 4 months, followed by 14.8 mg/m^3 for 4 months, and 9.4 mg/m^3 for 16 months). Following the 2-year exposure, the rats were held without TiO_2 exposure for 6 months [Heinrich et al. 1995]. The primary particle size range was 15 to 40 nm, and the MMAD particle size was 0.8 μm, which consisted of agglomerates of individual ultrafine particles. A statistically significant increase in adenocarcinomas was observed (13 adenocarcinomas, 3 squamous cell carcinomas, and 4 adenomas in 100 rats). In addition, 20 rats had benign keratinizing cystic squamous-cell tumors. Only 1 adenocarcinoma, and no other lung tumors, was observed in 217 nonexposed control rats.

In Heinrich et al. [1995], mice were also exposed to ultrafine TiO_2. The lifespan of NMRI mice was significantly decreased by inhaling approximately 10 mg/m^3 ultrafine TiO_2 18 hr/day for 13.5 months [Heinrich et al. 1995]. This exposure did not produce tumors in NMRI mice, but a 30% lung tumor prevalence in controls may have decreased the sensitivity of this strain for detecting carcinogenic effects.

3.3.2 Chronic Oral

The National Cancer Institute (NCI) conducted a bioassay of TiO_2 for possible carcinogenicity by the oral route. TiO_2 was administered in feed to Fischer 344 rats and B6C3F$_1$ mice. Groups of

50 rats and 50 mice of each sex were fed either 25,000 or 50,000 parts per million (ppm) TiO_2 for 103 weeks and then observed for 1 additional week. In the female rats, C-cell adenomas or carcinomas of the thyroid occurred at incidences that were dose related (P=0.013), but were not elevated enough (P=0.043 for direct comparison of the high-dose group with the control group) to attain statistical significance at the level of P=0.025 required by the Bonferroni criterion [Piegorsch and Bailer 1997]. The tumor incidence was 1/48 in the controls, 0/47 in the low-dose group, and 6/44 in the high-dose group. It should also be noted that a similar incidence of C-cell adenomas or carcinomas of the thyroid as observed in the high-dose group of the TiO_2 feeding study has been seen in control female Fischer 344 rats used in other studies. No significant excess tumors occurred in male or female mice or in male rats. It was concluded that under the conditions of this bioassay, TiO_2 is not carcinogenic by the oral route for Fischer 344 rats or $B6C3F_1$ mice [NCI 1979].

3.4 RAT AS A MODEL FOR HUMAN INHALATION RISKS

3.4.1 Rodent Lung Responses to Fine and Ultrafine TiO_2

Both fine and ultrafine TiO_2 are capable of eliciting pulmonary inflammation in the rat. Ultrafine TiO_2 was more damaging to the rodent lung than fine TiO_2. For example, 24 hr after intratracheal instillation of 500 μg of ultrafine or fine TiO_2, only the rats instilled with ultrafine TiO_2 had elevations in the neutrophil percentage, γ-glutamyl transpeptidase concentration (a measure of cell damage), and protein concentration in fluid (BALF) [Renwick et al. 2004]. Subchronic inhalation of ultrafine TiO_2 was also more inflammatory and more fibrogenic than inhalation of fine TiO_2. Rats inhaling 23.5 mg/m^3 ultrafine TiO_2, 6 hr/day, 5 days/week, for 12 weeks developed more pulmonary fibrosis than rats inhaling fine TiO_2 under comparable

exposure concentrations [Baggs et al. 1997]. Rats and mice inhaling 10 mg/m^3 ultrafine TiO_2 have impaired particle clearance after approximately 3 months of exposure, which persists with or without exposure cessation [Heinrich et al. 1995; Bermudez et al. 2004]. In contrast, no impaired particle clearance was seen in hamsters inhaling 10 mg/m^3 ultrafine TiO_2, 6 hr/day, for 13 weeks. Rats and mice inhaling 10 mg/m^3 ultrafine TiO_2 for 13 weeks have significantly elevated numbers of neutrophils, macrophages, and lymphocytes in BALF [Bermudez et al. 2004]. Numbers of macrophages and neutrophils in the BALF of ultrafine TiO_2-exposed rats returned to control levels at 13 and 26 weeks after exposure cessation, respectively. Conversely, in ultrafine TiO_2-exposed mice, numbers of macrophages and neutrophils in the BALF persisted throughout the maximum study recovery period of 52 weeks [Bermudez et al. 2004].

Altered proliferation of alveolar epithelium was observed in both rats and mice inhaling 10 mg/m^3 ultrafine TiO_2, although rats were affected at earlier timepoints. After inhaling 10 mg/m^3 fine TiO_2 for 13 weeks, the alveolar cell replication index of mice was significantly increased at 13 and 26 weeks after exposure cessation [Bermudez et al. 2004]. Rats exposed to 2 or 10 mg/m^3 ultrafine TiO_2 for 13 weeks showed an increase in the alveolar replication index immediately after exposure; in rats exposed to 10 mg/m^3 ultrafine TiO_2 the increased replication index persisted at 4 and 13 weeks after exposure cessation [Bermudez et al. 2004]. The major histopathologic alterations observed in the lungs of rats exposed to approximately 10 mg/m^3 ultrafine TiO_2 for up to 2 years were bronchioloalveolar hyperplasia and mild interstitial fibrosis [Heinrich et al. 1995].

Both fine and ultrafine TiO_2 are fibrogenic and carcinogenic in the lungs of chronically exposed rats. Pulmonary interstitial fibrosis developed in rats exposed to 50 or 250 mg/m^3 fine TiO_2 6 hr/day for 2 years [Lee et al. 1985, 1986a]. Rats inhaling approximately 10 mg/m^3 ultrafine TiO_2 18 hr/day for 2 years had pulmonary interstitial fibrosis [Heinrich et al. 1995]. Exposure to approximately 10 mg/m^3 ultrafine TiO_2 18 hr/day for 18 or 24 months also caused a significantly increased number of lung tumors in rats [Heinrich et al. 1995]. Similarly, rats inhaling 250 mg/m^3 fine TiO_2 6 hr/day for 2 years developed lung tumors [Lee et al. 1985, 1986a].

Lung tumors in rats exposed to TiO_2 have been described as benign squamous cysts, bronchoalveolar adenomas, squamous cell carcinomas, and adenocarcinomas [Lee et al. 1985; Heinrich et al. 1995]. The significance of the rodent benign squamous cysts (proliferative keratin cysts, cystic keratinizing squamous lesions of the rat lung) for human risk assessment has been debated [Carlton 1994; Boorman et al. 1996]. In fact, many pathologists consider the rat lung squamous cell keratinizing tumor to be irrelevant to human lung pathology. However, the pulmonary adenomas and adenocarcinomas seen in TiO_2-exposed rats are similar to pulmonary neoplasms in humans [Maronpot et al. 2004]. For purposes of conducting a quantitative risk assessment, NIOSH analyzed the risks both with and excluding the keratinizing cysts (see Appendix D) whenever it was possible to do so; i.e., whenever the available data provided sufficient information to separate keratinizing cysts from other pulmonary tumors.

3.4.2 Lung Overload

It has been argued that inhalation dose-response data from rats exposed to PSLT particles should not be used in extrapolating cancer risks to humans because the lung tumors in rats have been

attributed to a rat-specific response to the overloading of particle clearance from the lungs [Watson and Valberg 1996; Hext et al. 2005]. However, the dose-response relationship for lung tumors in rats has been shown to be statistically significantly associated with the total particle surface area at all doses (Figures 3-3 and 3-4), which indicates that the lung tumor response of PSLT can be predicted by the particle surface area dose without the need to account for overloading. In addition, lung clearance of particles is slower in humans than in rats, by approximately an order of magnitude [Hseih and Yu 1998], and some humans (e.g., coal miners) may be exposed to concentrations resulting in doses that would be considered overloaded in rats. Thus, the doses that cause overloading in the rat may be relevant to estimating disease risk in workers with high dust exposures.

Studies have shown that rats are more sensitive than mice or hamsters to developing lung tumors from exposure to PSLT particles [Bermudez et al. 2002, 2004]; however, hamsters have more rapid lung clearance and did not retain comparable amounts of dust in the lungs. Also, mice and hamsters are known to give false negatives in bioassays for some human carcinogens [Mauderly 1997]. The more relevant question is how sensitive is the rat to developing lung cancer from exposure to TiO_2 when compared quantitatively with humans. No direct evidence sheds light on the relative sensitivity of rats and humans to the carcinogenic effects of TiO_2, but evidence from known human carcinogens, such as asbestos and crystalline silica, suggests that rats are no more sensitive to these effects than are humans.

3.4.3 Dose Metric

Pulmonary response to TiO_2 in the rat is correlated better to particle surface area than to mass, for both cancer and noncancer response, including pulmonary inflammation. This relationship between particle surface area and noncancer responses has been shown by Oberdörster et al. [1992] for rats exposed to fine or ultrafine TiO_2 by intratracheal instillation and in rats exposed by inhalation of fine TiO_2 or $BaSO_4$ for up to 7 months [Tran et al. 1999]. Höhr et al. [2002] observed that, for the same surface area, the inflammatory response (as measured by bronchoalveolar lavage fluid markers of inflammation) of uncoated TiO_2 particles covered with surface hydroxyl groups (hydrophilic surface) was similar to that of TiO_2 particles with surface OCH_3-groups (hydrophobic surface) replacing OH-groups. The relationship between particle surface area and lung tumors, first shown by Oberdörster and Yu [1990], was extended by Driscoll [1996] to include results from subsequent chronic inhalation studies in rats exposed to PSLT particles and by Miller [1999] who refit these data using a logistic regression model. Although these various types of PSLT particles showed separate dose-response relationships on a mass basis, a single dose-response relationship fit all particle types when dose was expressed as total particle surface area (Figure 3-4).

The dose-response data for the three chronic inhalation studies of TiO_2 are shown in Figures 3-5 and 3-3. In these figures, the tumor response data are shown separately for male and female rats at 24 months in Lee et al. [1985] and for female rats at 24 or 30 months, including either all tumors or tumors without keratinizing cystic tumors [Heinrich et al 1995] (all data available from the paper are plotted). The data are plotted per gram of lung to adjust for differences in the lung mass in the two strains of rats (Sprague-Dawley and Wistar). Figure 3-5 shows that when TiO_2 is

expressed as mass dose, the lung tumor response to ultrafine TiO_2 is much greater than that for fine TiO_2; yet when TiO_2 is expressed as particle surface area dose, both fine and ultrafine TiO_2 data fit the same dose-response curve (Figure 3-3). Therefore, a sufficient particle surface area dose of fine TiO_2 would be expected to be carcinogenic; however, this would require a much higher mass dose of fine particles than ultrafine particles.

3.5 COMPARISON OF RODENT AND HUMAN LUNG RESPONSES TO INHALED PARTICLES

3.5.1 Lung Tissue Responses

Comparing the effects of fine TiO_2 inhalation in humans and laboratory animals reveals a number of similarities. In both human and animal studies, respirable TiO_2 persisted in the lung. The extensive pulmonary deposition seen in some workers years after ceasing TiO_2 exposure [Määttä and Arstila 1975; Rode et al. 1981] appears to be more consistent with the slow TiO_2 clearance observed in heavily exposed rats and mice than the rapid clearance pattern observed in hamsters [Everitt et al. 2000; Bermudez et al. 2002].

Inflammation, observed in lung tissue at pathological examination, was associated with deposited titanium in the majority of human cases with heavy TiO_2 deposition in the lung [Elo et al. 1972; Rode et al. 1981; Yamadori et al. 1986; Moran et al. 1991]. Pulmonary inflammation has also been observed in studies in rats, mice and hamsters exposed to TiO_2 [Lee et al. 1985, 1986a; Everitt et al. 2000; Bermudez et al. 2002]. Continued pulmonary inflammation in the lung of some exposed workers after exposure cessation [Määttä and Arstila 1975; Rode et al.

1981] is more consistent with the findings in rats and mice than in hamsters, where inflammation gradually resolved with cessation of exposure.

The one case of life-threatening lipoproteinosis seen in a worker with high pulmonary deposition of TiO_2 [Keller et al. 1995] was more severe than seen in any exposed laboratory animals, although alveolar lipoproteinosis was also observed in TiO_2-exposed rats [Lee et al. 1985, 1986a; Bermudez et al. 2002]. Similarly, mild fibrosis reported in the lungs of workers exposed to TiO_2 [Elo et al. 1972; Moran et al. 1991; Yamadori et al. 1986] was reported in rats with chronic inhalation exposure to TiO_2 [Heinrich et al. 1995; Lee et al. 1985, 1986a]. Alveolar metaplasia has been briefly described in three human patients whose major common exposure was TiO_2 [Moran et al. 1991]. In laboratory animals, alveolar metaplasia was only described in the rats [Lee et al. 1985; Everitt et al. 2000; Bermudez et al. 2004]. However, similarities and differences between the alveolar metaplastic changes of the rat and human have not been clarified.

3.5.2 Role of Chronic Inflammation in Lung Disease

Studies in animals and humans have shown associations between chronic pulmonary inflammation and lung disease [Castranova 1998, 2000; Marx 2004; Katabami et al. 2000]. Chronic inflammation is characterized by persistent elevation of the number of polymorphonuclear leukocytes (PMNs) (measured in BALF) or by an increased number of inflammatory cells in interstitial lung tissue (observed by histopathology).

In rats exposed by inhalation to various types of particles, elevation in PMNs is associated with the overloading of alveolar macrophage-mediated clearance [Donaldson et al. 1988; Morrow 1998; Tran et al. 1999, 2000] and with fibrosis and lung tumors [Oberdörster and Yu 1990; Driscoll 1996; Oberdörster 1996]. In addition, interstitial inflammation (i.e., inflammatory cells in lung tissue) has been related to increased tumor incidence in rats exposed by instillation to various types of particles [Borm et al. 2000]. Particle surface area dose was shown in those studies to be a better predictor of these effects than was mass dose for various types of PSLT respirable particles.

In humans, chronic inflammation has been associated with non-neoplastic lung diseases in workers with dusty jobs. Rom [1991] found a statistically significant increase in the percentage of PMNs in BALF of workers with respiratory impairment who had been exposed to asbestos, coal, or silica (4.5% PMN in cases versus 1.5% PMNs in controls). Elevated levels of PMNs have been observed in the BALF of miners with simple coal workers' pneumoconiosis (31% of total BAL cells versus 3% in controls) [Vallyathan et al. 2000] and in patients with acute silicosis (also a 10-fold increase over controls) [Lapp and Castranova 1993; Goodman et al. 1992]. Humans with lung diseases that are characterized by chronic inflammation and epithelial cell proliferation (e.g., idiopathic pulmonary fibrosis; diffuse interstitial fibrosis associated with pneumoconiosis) have an increased risk of lung cancer [Katabami et al. 2000]. Dose-related increases in lung cancer have been observed in workers exposed to respirable crystalline silica [Rice et al. 2001; Attfield and Costello 2004], which can cause inflammation and oxidative tissue damage [Castranova 2000]. Chronic inflammation appears to be important in the etiology of dust-related lung disease, not only in rats, but also in humans with dusty jobs [Castranova 1998, 2000]. Studies of nonmalignant lung disease in TiO_2 workers have been limited, although some

case studies have reported lung responses indicative of inflammation, including alveolar proteinosis [Keller et al. 1995] and interstitial fibrosis [Yamadori et al. 1986; Moran et al. 1991; Elo et al. 1972] in workers (in which the lungs contained TiO_2 and other minerals).

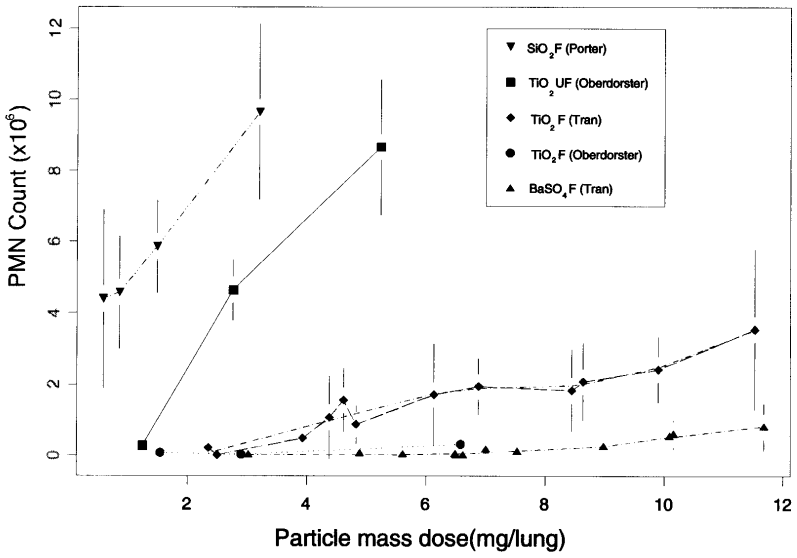
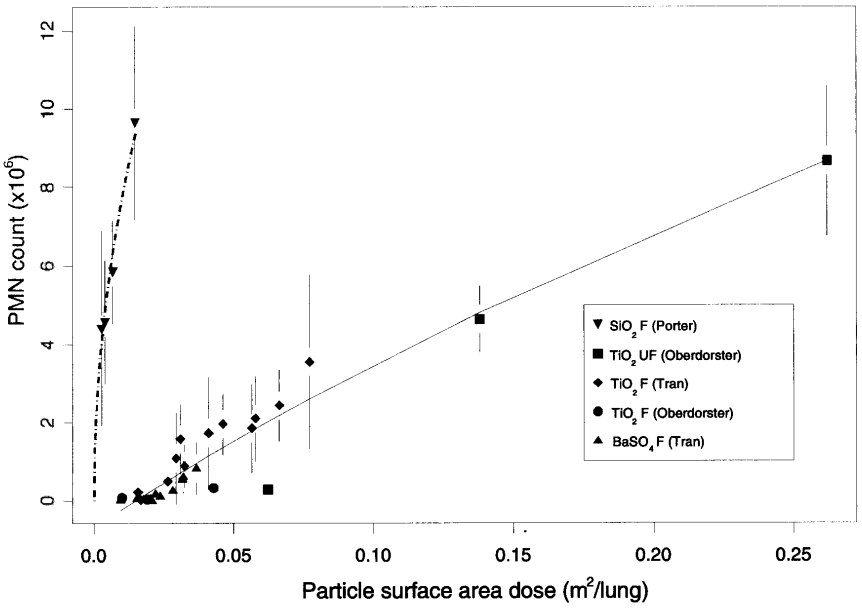


Figure 3-1. Pulmonary inflammation (PMN count) of high toxicity dust (crystalline silica) particles compared to low toxicity dust (TiO_2 and $BaSO_4$) of both fine and ultrafine size, based on particle mass dose in rat lungs. Data from: Porter et al. [2001]; Oberdörster et al. [1994]; Tran et al. [1999]. Particle size: F (fine); UF (ultrafine).



1129
1130
1131 **Figure 3-2. Pulmonary inflammation (PMN count) of high toxicity dust (crystalline silica)**
1132 **particles compared to low toxicity dust (TiO_2 and $BaSO_4$) of both fine and ultrafine size --**
1133 **based on particle surface area dose in rat lungs. Data from: Porter et al. [2001];**
1134 **Oberdörster et al. [1994]; Tran et al. [1999]. Particle size: F (fine); UF (ultrafine).**
1135

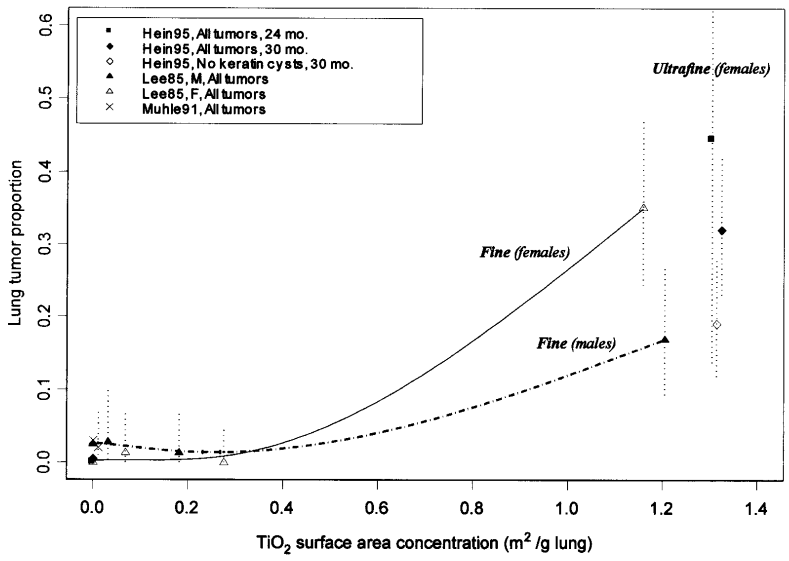
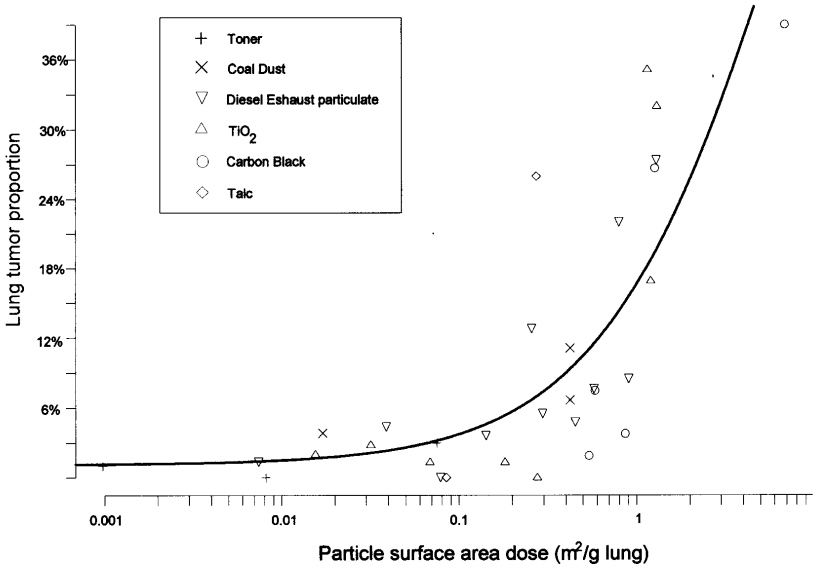


Figure 3-3. TiO_2 surface area dose in the lungs of rats exposed by inhalation for two years and tumor proportion (either all tumors, or tumors excluding keratinizing squamous cell cysts). Data from Heinrich et al. [1995], Lee et al. [1985, 1986a], and Muhle et al. [1991]. Spline model fits to Lee data. (Heinrich dose data are *jittered*, i.e., staggered).



1168
1169
1170
1171 **Figure 3-4. Relationship between particle surface area dose in the lungs of rats after**
1172 **chronic inhalation to various types of poorly soluble low toxicity (PSLT) particles and**
1173 **tumor proportion (all tumors including keratinizing squamous cell cysts). *Data from*:**
1174 **Toner [Muhle et al. 1991]; coal dust [Martin et al. 1977]; diesel exhaust particulate**
1175 **[Mauderly et al. 1987; Lewis et al. 1989; Nikula et al. 1995; and Heinrich et al. 1995];**
1176 **Titanium dioxide (TiO_2) [Muhle et al. 1991; Heinrich et al. 1995; Lee et al. 1985, 1986a];**
1177 **Carbon black [Nikula et al. 1995; Heinrich et al. 1995]; talc [NTP 1993].**
1178

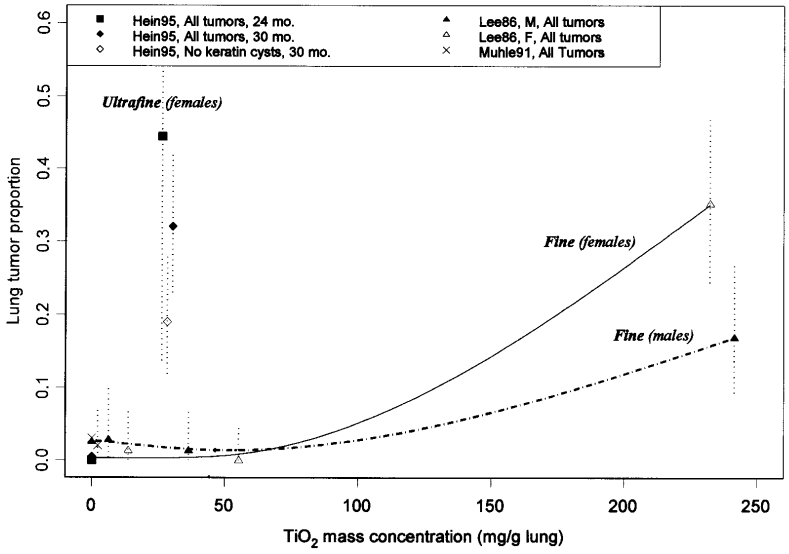


Figure 3-5. TiO_2 mass dose in the lungs of rats exposed by inhalation for two years and tumor proportion (either all tumors, or tumors excluding keratinizing squamous cell cysts). Data from Heinrich et al. [1995], Lee et al. [1985, 1986a], and Muhle et al. [1991]. Spline model fits to Lee data. (Heinrich dose data are *jittered*, i.e., staggered).

4. QUANTITATIVE RISK ASSESSMENT

4.1 INTRODUCTION

4.1.1 Data and Approach

For quantitative risk assessment, dose-response data are needed, either from human studies or extrapolated to humans from animal studies. The epidemiologic studies on lung cancer have not shown a dose-response relationship in TiO_2 workers [Fryzek et al. 2003; Boffetta et al. 2004]. However, dose-response data are available in rats, for both cancer (lung tumors) and early, noncancer (pulmonary inflammation) endpoints. The lung tumor data were from chronic inhalation studies and included three dose groups for fine TiO_2 and one dose group (in addition to controls) for ultrafine TiO_2. The pulmonary inflammation data were from subchronic inhalation studies of fine particles, and included one or two dose groups of fine TiO_2 [Tran et al. 1999; Cullen et al. 2002]. Various modeling approaches were used to fit these data and to estimate the risk of disease in workers exposed to TiO_2 for up to a 45-year working lifetime.

The modeling results from the rat dose-response data provide the quantitative basis for developing the recommended exposure limits (RELs) for TiO_2, while the mechanistic data from rodent and human studies (Chapter 3) provide scientific information on selecting the risk assessment models and methods. The practical aspects of mass-based aerosol sampling and analysis were also considered in the overall approach (i.e., the conversion between particle surface area for the rat dose-response relationships and mass for the human dose estimates and recommended exposure limits). Figure 4-1 illustrates the risk assessment approach.

4.1.2 Methods

Statistical dose-response modeling was used to estimate the retained particle burden in the lungs associated with lung tumors or pulmonary inflammation. Both maximum likelihood and 95% lower CI estimates of the internal lung doses in rats were computed. Particle surface area was the dose metric used in these models because it has been shown to be a better predictor than particle mass of both cancer and noncancer responses in rats (Chapter 3). In the absence of quantitative data comparing rat and human lung responses to TiO_2, rat and human lung tissue were assumed to have equal sensitivity to an equivalent particle surface area dose. Human lung dosimetry models [CIIT and RIVM 2002; Kuempel et al. 2001a,b; Tran and Buchanan 2000] were used to estimate the working lifetime airborne mass concentrations associated with the critical doses in the lungs, as identified from the rat dose-response data. The term "critical dose" is defined as the retained particle dose in the rat lung (MLE or 95% LCL) associated with a specified response, including either initiation of inflammation or a given excess risk of lung cancer.

One measure of critical dose for lung cancer is the *benchmark* dose, which has been defined as ". . . a statistical lower confidence limit on the dose corresponding to a small increase in effect over the background level" [Crump 1984]. This is typically at 5% or 10% excess risk, within the range of the data, where various models all predict similar risks. In current practice, and as used in this document, the benchmark dose (BMD) refers to the maximum likelihood estimate (MLE) from the model; and the benchmark dose low (BMDL) is the 95% lower confidence limit of the BMD [Gaylor et al. 1998], which is equivalent to the BMD as originally defined by Crump [1984]. Another measure of critical dose was the estimated threshold dose derived from a

piecewise linear model fit to the noncancer data (pulmonary inflammation data) (Appendix B). A final approach to estimating critical lung doses was to determine the doses associated with specified levels of excess risk (e.g., 0.001, or 1 excess case per 1,000 workers exposed over a 45-year working lifetime), either estimated directly from a selected model or by linear extrapolation from the BMD.

The critical doses were derived using particle surface area, which was estimated from the mass lung burden data and from measurements or estimates of specific surface area (i.e., particle surface area per mass). These critical particle surface area doses were converted back to particle mass dose when extrapolating to humans because the current human lung dosimetry models (used to estimate airborne concentration leading to the critical lung doses) are all mass-based, and because the current occupational exposure limits for most airborne particulates including TiO_2 are also mass-based.

In summary, the dose-response data in rats were used to determine the critical dose, as particle surface area in the lungs, associated with pulmonary inflammation or lung tumors; and the excess risks associated with those critical doses were estimated from statistical modeling of the rat data. The working lifetime airborne mass concentrations associated with the human-equivalent critical lung burdens were estimated using human lung dosimetry models. The results of these quantitative analyses, and the derivation of the RELs for fine and ultrafine TiO_2, are provided in the remainder of this chapter.

4.2 DOSE-RESPONSE MODELING OF RAT DATA AND EXTRAPOLATION TO HUMANS

4.2.1 Pulmonary Inflammation

4.2.1.1 Rat data

Data from two different subchronic inhalation studies in rats were used to investigate the relationship between particle surface area dose and pulmonary inflammation response: (1) TiO_2 used as a control in a study of the toxicity of volcanic ash [Cullen et al. 2002] and (2) fine TiO_2 and $BaSO_4$ in a study of the particle surface area as dose metric [Tran et al. 1999]. Details of these studies are provided in Table 4-1. Since only male Wistar rats were used in these studies, no adjustment for lung weight differences across rat strain and sex was necessary. Individual rat data were obtained for PMN count in the lungs in each study. In the Tran et al. [1999] study, a different group of rats was used to estimate lung burden, while in the Cullen et al. [2002] study, the same rats were used for both measures (i.e., PMN and lung burden data obtained for each individual rat).

4.2.1.2 Critical dose estimation in rats

The data of TiO_2 lung dose and pulmonary inflammation from the Tran et al. [1999] and Cullen et al. [2002] studies were not homogeneous in that a single dose-response curve would not adequately fit both sets of data. Although the shape of the dose-response relationship was similar (i.e., nonlinear, with no detectable elevation in response at low doses, followed by increasing inflammation response at doses greater than a certain "critical" dose), the doses associated with the beginning of inflammation were significantly different. Therefore, the data

from these two studies were fit separately by a piecewise linear model, and the threshold parameter was estimated separately.

Continuous models in the BMDS suite [EPA 2003] were also fit to these pulmonary inflammation data, but these models either did not converge or failed to provide an adequate fit to either set of TiO_2 data (i.e., *P*-values <0.05 in lack of fit tests). In those models (including linear, quadratic, and power models with nonconstant variance), the critical dose or BMD was defined as the particle surface area dose in the lungs associated with a mean inflammatory response corresponding to the upper 5th percentile of the distribution of PMN counts in control rat lungs.

In contrast, a piecewise linear model that included a threshold parameter did fit the data; and this threshold parameter was significant at a 95% confidence level.* In this model, the threshold dose (maximum likelihood and CI estimates) was considered the critical dose. This critical dose is not analogous to the BMD defined above since the piecewise linear model assumes no excess risk below the critical (threshold) dose, while the BMD models assume a specified level of excess risk at the critical dose. Excess risk is the risk that is attributable to the exposure, or the additional risk above the *background* risk from other causes. The piecewise linear model is described in more detail in Appendix B.

* The significance of the threshold parameters was validated using bootstrap methods; however, it should be noted that the parameter is significant under the model assumption of linearity in the dose-response. Thus, one cannot generalize this statement beyond linearity and assume that the threshold is significant among a larger class of models.

Figure 4-2 shows a piecewise linear model fit to the TiO_2 particle surface area dose and the PMN count [Tran et al. 1999]. For comparison, it also shows a linear model fit to the data. Figure 4-3 shows the same model fit to another TiO_2 data set [Cullen et al. 2002] (note that the x-axis scales differ in Figures 4-2 and 4-3). The probability that these thresholds would be observed if the true relationship was linear was less than 0.01.

Using the piecewise linear model fit to the data shown in Figures 4-2 and 4-3, critical dose estimates were derived for the particle surface area dose of TiO_2. Table 4-2 shows these estimates. The MLE of the threshold dose was 0.0134 m^2 for TiO_2 alone (0.0109 m^2 95% LCL) based on data from Tran et al. [1999]. A higher MLE threshold dose of 0.0409 was estimated from the TiO_2 data in Cullen et al. [2002]. The reason for the difference in the estimated critical dose for pulmonary inflammation (i.e., rise in PMN count) in these two data sets is not known, although there were differences in study design (Table 4-1), including using the same versus different rats for measuring lung burden and response, as mentioned above. The difference in inhalation exposure method (whole body vs. nose only) seems unlikely to have influenced the dose-response relationship because the retained lung burden data were used for each, unless the different techniques resulted in different rates or patterns of dose that may have influenced tissue response.

4.2.1.3 Estimating human equivalent exposure

The critical dose estimates from Table 4-3 were converted to mass dose and extrapolated to humans by adjusting for species differences in lung mass. This is explained further in the context of the rat lung tumor data (Section 4.2.2.3). Also, as described in that section, human lung

dosimetry models were used to estimate the airborne concentrations of either fine or ultrafine TiO_2 over a 45-year working lifetime that would be associated with an increase in pulmonary inflammation, derived from the rat data.

4.2.2 Lung Tumors

4.2.2.1 Rat data

Dose-response data from chronic inhalation studies in rats exposed to TiO_2 were used to estimate working lifetime exposures and lung cancer risks in humans. These studies are described in more detail in Table 4-4, and include fine (pigment-grade) rutile TiO_2 [Lee et al. 1985; Muhle et al. 1991] and ultrafine anatase TiO_2 [Heinrich et al. 1995]. The doses for fine TiO_2 include: 5 mg/m^3 (74% respirable) [Muhle et al. 1991]; and 10, 50, and 250 mg/m^3 [Lee et al. 1985]. For ultrafine TiO_2, there was a single dose of approximately 10 mg/m^3 TiO_2. Each of these studies reported the retained particle mass lung burdens in the rats. The internal dose measure of particle burden at 24 months of exposure was used in the dose-response models, either as particle mass or particle surface area (calculated from the reported or estimated particle surface area).

Only the Heinrich et al. [1995] study reported a specific surface area (48 ± 2 m^2/g ultrafine TiO_2) for the airborne particulate, as measured by the Brunaeur, Emmett, and Teller (BET) N_2 adsorption method. For the Lee et al. [1985] study, the specific surface area (4.99 m^2/g fine TiO_2) reported by Driscoll [1996] was used; that value was based on measurement of the specific surface area of a rutile TiO_2 sample similar to that used in the Lee study [Driscoll 2002]. This specific surface area was also assumed for the fine TiO_2 in the Muhle et al. [1991] study.

1371 The relationship between particle surface area dose of either fine or ultrafine TiO_2 and lung
1372 tumor response (including all tumors or tumors excluding the squamous cell keratinizing cysts)
1373 in male and female rats was shown in Chapter 3. Statistically significant increases in lung
1374 tumors were observed at the highest dose of fine TiO_2 (250 mg/m^3) or ultrafine TiO_2
1375 (approximately 10 mg/m^3), whether or not the squamous cell keratinizing cysts were included in
1376 the tumor counts.
1377
1378 Different strain and sex of rats were used in each of these three TiO_2 studies. The Lee et al.
1379 [1985] study used male and female Sprague-Dawley rats (crl:CD strain). The Heinrich study
1380 used female Wistar rats [crl:(WI)BR strain]. The Muhle et al. [1991] study used male and female
1381 Fischer-344 rats but reported only the average of the male and female lung tumor proportions.
1382 The body weights and lung weights differed by rat strain and sex (Table 4-4). These lung mass
1383 differences were taken into account when calculating the internal doses, either as mass (mg
1384 TiO_2/g lung tissue) or surface area (m^2 TiO_2/g lung tissue).
1385

1386 ***4.2.2.2 Critical dose estimation in rats***

1387 Statistical models for quantal response were fit to the rat tumor data, including the suite of
1388 models in the BMDS [EPA 2003]. The response variable used was either all lung tumors or
1389 tumors excluding squamous cell keratinizing cystic tumors. Figure 4-4 shows the fit of the
1390 various BMD models [EPA 2003] to the lung tumor response data (without squamous cell
1391 keratinizing cysts) in male and female rats chronically exposed to fine or ultrafine TiO_2 [Lee et
1392 al. 1985; Heinrich et al. 1995].
1393

The lung tumor response in male and female rats was significantly different for "all tumors" but not when squamous cell keratinizing cystic tumors were removed from the analysis (Appendix C, Table C-2). In other words, the male and female rat lung tumor responses were equivalent except for the squamous cell keratinizing cystic tumor response, which was elevated only in the female rats. To account for the heterogeneity in the "all tumor" response among male and female rats [Lee et al. 1985; Heinrich et al. 1995], a modified logistic regression model was developed (Appendix A); this model also adjusted for the combined mean tumor response for male and female rats reported by Muhle et al. [1991]. As discussed in Chapter 3, many pathologists consider the rat lung squamous cell keratinizing cystic tumor to be irrelevant to human lung pathology. Excess risk estimates of lung tumors were estimated both ways – either with or without the squamous cell keratinizing cystic tumor data. The full results of the analyses including squamous cell keratinizing cystic tumors can be found in Appendix D. Inclusion of the keratinizing cystic tumors in the analyses resulted in slightly higher excess risk estimates in females, but not males.

The estimated particle surface area dose associated with either a 1/10 or 1/1000 excess risk of lung tumors is shown in Table 4-5 for lung tumors excluding squamous cell keratinizing cystic lesions. The 1/1000 excess risk BMD and BMDL estimates were derived using two approaches: (1) linear extrapolation from the 1/10 excess risk BMD and BMDL estimates (where all models provided similar estimates) [Crump 1984], and (2) estimates for 1/1000 excess risk derived directly from each model; these different model estimates were then summarized using a Bayesian model averaging approach [Bailer et al. 2005]. The linearized multistage model was used as an example of an individual model.

1417

1418 These various models were also fit to the all tumor rat data. The results were similar and are
1419 provided in Appendix D. The male and female rat data could be combined for the models of lung
1420 tumors without the keratinzing cystic tumors; however, due to heterogeneity by rat sex for the *all*
1421 *lung tumor* response, the BMDS models [EPA 2003] were fit separately to the male and female
1422 rat data (Appendix D). In addition, a logistic model was developed to account for the differences
1423 in response for males and females (Appendix A), which allowed all of the data to be used in one
1424 overall model. The estimates from that logistic model were also similar (Appendix D). The 95%
1425 CIs were based on a profile likelihood method [Crump 1984]. The lower confidence limits on
1426 dose and the upper confidence limits on excess risk are reported because these are of primary
1427 interest for risk assessment.
1428
1429 The highest estimates for particle surface area dose associated with 1/1000 excess risk of lung
1430 cancer were derived from the direct model estimates (Table 4-5), which shows that the BMD and
1431 BMDL vary considerably depending on the shape of the model in the low dose region. When
1432 these model-based estimates were summarized using Bayesian model averaging (BMA), the
1433 BMA estimate was also higher than estimates derived from linear extrapolation from the 1/10
1434 BMD and BMDL, reflecting the curvature of the best-fitting models. BMA provides an approach
1435 for summarizing the risk estimates from the various models, which differ in the low-dose region
1436 of interest for human health risk estimation. BMA also provides an approach for addressing the
1437 uncertainty in choice of model in the BMD approach. Because the best-fitting models in this case
1438 contained significant curvature and the models are used directly to estimate excess risk, the

associated doses tend to be higher than those that would be estimated from a low-dose linear model, or from a benchmark dose with linear extrapolation.

4.2.2.3 Estimating human equivalent exposure

Table 4-6 provides estimates of the airborne concentrations of either fine or ultrafine TiO_2 over a 45-year working lifetime that are associated with a 1/1000 excess risk of lung cancer. As expected, the mass airborne concentrations associated with a given surface area dose in the lungs is lower for ultrafine TiO_2 than for fine TiO_2. The differences in fine and ultrafine mass concentration estimates are nearly proportional to the differences in specific surface area. In addition, slight differences in the lung deposition fraction for inhaled fine TiO_2 and ultrafine TiO_2 (as agglomerates) contribute; however, the major factor influencing the mass concentration estimates is the difference in surface area of fine versus ultrafine TiO_2 for a given mass.

The published BET-measured specific surface area data for fine and ultrafine TiO_2 were used to convert from particle mass to surface area dose when extrapolating the rat-based critical dose estimates to humans. These measured values were 6.68 m^2/g for fine (Tran et al. [1999]) and 48 m^2/g for ultrafine TiO_2 (Heinrich et al. [1995]). Data were not available on the airborne TiO_2 particle size distributions in the workplace. In the absence of workplace exposure data, these published measured values were used to represent the fine and ultrafine particle size fractions and to estimate the working lifetime exposures associated with critical doses (i.e., those associated with initiation of pulmonary inflammation or a specified excess risk of lung tumors—based on rat data extrapolated to humans). The excess risk estimates will vary for other particle sizes and surface areas. The observed particle surface area dose-response relationship indicates

that within either the fine or ultrafine size categories, if workers inhale particles with greater specific surface areas than those used to develop the RELs, then the excess risks would be expected to be higher. Similarly, if workers inhale particles with lower specific surface areas than those used to develop the RELs, then the excess risks would be expected to be lower. Characterizing the airborne TiO_2 particle sizes to which workers may be exposed is a critical research need (Chapter 7).

The choice of dosimetry model also influences the estimates of the mean airborne concentration. A major difference between the multi-path model of particle deposition (MPPD) model of CIIT and RIVM [2002] and the interstitialization/sequestration model [Kuempel et al. 2001a,b; Tran and Buchanan 2000] is that the latter includes a biologically-based structure to specifically account for the retention of particles in the lungs, as observed in coal miners, while the former uses the International Commission on Radiological Protection (ICRP) [1994] alveolar clearance model that has three separate first-order clearance compartments to approximate particle retention. Yet, in a comparison of several different human lung dosimetry models, the ICRP [1994] alveolar clearance model was reasonably close to the interstitial/sequestration model in predicting the lung burdens in coal miners [Kuempel and Tran 2002]. The MPPD model [CIIT and RIVM 2002] provides a choice of several deposition models, and the default selection of Yeh/Schum Symmetric was used for these calculations. The MPPD deposition model [CIIT and RIVM 2002] account for variability in the particle size distribution, while the interstitialization/sequestration model uses the deposition fractions from the ICRP [1994] model for the mean particle diameter. The interstitial/sequestration model was developed and calibrated using data of U.S. coal miners [Kuempel et al. 2001a,b] and later validated using data of U.K.

coal miners [Tran and Buchanan et al. 2000]. The ICRP [1994] model was developed using data on the clearance of radiolabeled tracer particles in humans, and it has been in use for many years.

More data are needed to evaluate the model structures and determine how well each model would describe the retained doses associated with low particle exposures in humans. In addition, the extent to which these models adequately describe the clearance and retention of ultrafine particles is needed (although particle deposition specifically considers particle size, the clearance of respirable particles, whether fine or ultrafine size, is mass-based in each of these models). Furthermore, none of these models specifically accounts for variability in the deposition and clearance of inhaled particles in humans (Kuempel et al. [2001b] provides an approach, given limited data).

Finally, the approach for extrapolating between rats and humans also influences the estimates of mean concentration in Table 4-6. To extrapolate the critical particle surface area dose in the lungs of rats to whole lungs in humans, either the relative mass or surface area of the lungs in each species was used. The results in Table 4-3 and 4-6 are based on the relative lung mass (assuming 1g for rat lung and 1000 g for human lungs). Alternatively, extrapolation could be based on relative lung surface area (e.g., 0.388 m^2 rat, 143 m^2 human [Parent 1992]), and in that case, the estimates of the working lifetime mean airborne concentrations in Tables 4-6 and 4-3 would be lower by a factor of approximately 1/3. The mass-based approach was used for the main analyses because data on lung mass was available in all rat strains used in the dose-response data, and these differences could be accounted for; in contrast, data on lung surface area by rat strain were not available. The lung mass of the Sprague-Dawley rats (used in the Lee et

al. [1985] study) was approximately twice that of the Wistar or Fisher 344 rats (used in the Heinrich et al. [1995] and Muhle et al. [1991] studies). Additional estimates of excess risk are provided using lung surface area adjustment to show how the excess risk estimates may vary based on alternative measures of scaling between rat and human lungs.

The critical dose estimates in Table 4-6 vary depending on the model used, including the dose-response models of the rat data and the human dosimetry lung models. Little difference was observed, however, between the MLE and the 95% lower confidence limit (LCL) estimates of the working lifetime mean concentrations because the BMD and BMDL estimates from the rat dose-response models were generally similar (except for the linearized multistage model, which has a much higher MLE due to that model form). It is likely that the 95% LCL values based on the rat data underestimate the true variability in the human population.

4.3 MECHANISTIC CONSIDERATIONS

The mechanism of action of TiO_2 is relevant to a consideration of the associated risks because, as discussed earlier, the weight of evidence suggests that the tumor response observed in rats exposed to fine and ultrafine TiO_2 results from a secondary genotoxic mechanism involving chronic inflammation and cell proliferation, rather than via genotoxicity of TiO_2 itself. This effect appears related to the physical form of the inhaled particle (i.e., particle surface area) rather than the chemical compound itself. In this way, TiO_2 behaves in a similar manner to other PSLT particles, such as barium sulfate, carbon black, toner, and coal dust (Figures 3-2 and 3-4).

Studies supporting this mechanism include empirical studies of the pulmonary inflammatory response of rats exposed to TiO_2 and other PSLT (including a piecewise linear model with a threshold parameter fit of the TiO_2 data) (Sections 3.2.3 and 4.2.1); the tumor response of TiO_2 and other PSLT, which have consistent dose-response relationships (Section 3.4.3); and in vitro studies, which show that inflammatory cells isolated from BALF from rats exposed to TiO_2 released reactive oxygen species that could induce mutations in naive cells (Section 3.2.1). There is some evidence, though limited, that inflammation may be a factor in human lung cancer, as well (Section 3.5.2).

In considering all the data, NIOSH has determined that a plausible mechanism of action for TiO_2 in rats can be described as the accumulation of TiO_2 in the lungs, overloading of lung clearance mechanisms, followed by increased pulmonary inflammation and oxidative stress, cellular proliferation, and, at higher doses, tumorigenesis. These effects are better described by particle surface area than mass dose (Section 3.4.3). The observed inflammatory response is consistent with a threshold mechanism (Section 4.2.1.2). The best-fitting dose-response curves for the tumorigenicity of TiO_2 are nonlinear (e.g., multistage model is cubic with no linear term) (Table 4-5), which would be consistent with a secondary genotoxic mechanism. This suggests that the carcinogenic potency of TiO_2 would decrease more than proportionately with decreasing *surface area* dose as described in the best-fitting risk assessment models.

4.4 RISK ESTIMATES

As discussed, the scientific evidence in rats suggests that the lung tumor mechanism associated with PSLT particles such as TiO_2 is a secondary, nongenotoxic mechanism involving chronic

inflammation and cell proliferation. In the absence of data in humans, a primary genotoxic mechanism cannot be ruled out, and the epidemiologic studies lacked the power to detect an excess risk of 1/1000. Furthermore, the threshold doses detected in the rat pulmonary inflammation data were in the same range as risk estimates derived from cancer risk modeling approaches for working lifetime exposures (Tables 4-3 and 4-6). This lends additional support to the selection of risks in the range of 1/1000 as critical risks. For these reasons, representative lung tumor modeling approaches were selected for further evaluation: linearized multistage modeling; BMD modeling with linear extrapolation; and BMA of all model estimates.

The linearized multistage model is a common approach that has been used frequently in cancer risk assessment.The BMD method targets a response probability that is within the range of the data, so that the estimate of the BMD is not sensitive to the choice of the model. In the case of TiO_2, this was a 10% tumor response. The lower bound on this dose is calculated and a straight line is drawn from the response at this lower bound for dose through zero to estimate risks at any dose of interest. This method ignores any curvature in the model-predicted dose-response relationship below the BMD.

An alternative to linear extrapolation from the BMD is to estimate the risks at doses of interest directly from the dose-response curve. Since the targeted excess risks are substantially smaller than 10%, the extrapolation of the dose-response curve to well below the range of the data is sensitive to the choice of model. When there is no clear mechanistically-based preference for one model over another, a way around this dilemma is to use model averaging techniques. These methods use all the information from the dose-response models, weighing each model by its

posterior probability of being the true model. The result is a weighted average of the fitted dose-response models. The question remains whether this is a better representation of the true model or whether it simply illustrates the impact of model uncertainty on the derived risk estimate summaries, but it gives the risk assessor the ability to summarize the dose-response behavior of the BMD Software Suite at low doses.

Each of these approaches was used to assess the excess risk of lung cancer at various working lifetime exposure concentrations of fine or ultrafine TiO_2 (Tables 4-7 and 4-8). As shown in Tables 4-7 and 4-8, selection of the model for estimating risks has a significant impact on the risk estimates. NIOSH believes that the three methods shown are all reasonable and supportable interpretations of the cancer exposure-response data.

As shown in Tables 4-7 and 4-8, the working lifetime mean concentration of *fine* TiO_2 associated with a <1/1000 excess risk of lung cancer is 1 to 5 mg/m^3, depending on the model used to fit the rat lung tumor data (based on either the 95% UCL or the Bayesian model average estimate). For *ultrafine* TiO_2, the working lifetime mean concentration associated with <1/1000 excess risk of lung cancer is <0.05 to 0.5 mg/m^3, depending on the rat model. The estimates in Tables 4-7 and 4-8 are based on modeling of the rat lung tumors excluding the squamous cell keratinizing cystic lesions.

The working lifetime mean concentrations shown in Tables 4-7 and 4-8 and estimated internal lung doses were also evaluated using the rat dose-response data on fine or ultrafine TiO_2 and pulmonary inflammation (Tables 4-9 and 4-10). The retained particle mass burden in human lungs after a 45-year working lifetime exposure to various airborne mean concentrations of TiO_2

were extrapolated to equivalent particle surface area dose in rat lungs. These rat-equivalent doses were then visually compared to the estimated 95% LCL on the threshold parameter for pulmonary inflammation in the rat (using a piecewise linear model and verified with bootstrapping, Appendix B). The bottom two rows in Tables 4-9 and 4-10 indicate whether the estimated lung burden associated with a given working lifetime mean concentration exceeds the 95% LCL estimate of the threshold dose from two different rat data sets [Tran et al. 1999; Cullen et al. 2002].

To compute the mean airborne concentration estimates in Tables 4-7 through 4-10, the MPPD human lung dosimetry model [CIIT and RIVM 2002] was used to estimate human lung doses associated with working lifetime exposures to a given mean concentration. The MPPD model [CIIT and RIVM 2002] includes the ICRP (1994) alveolar clearance model. These dose estimates were lower by a factor of approximately two compared to a model that includes interstitialization/sequestration of particles in the lungs [Kuempel et al. 2001a; Tran and Buchanan 2000]. The rat lung dose was extrapolated from the dosimetry model-estimated human lung dose, by adjusting for species differences in lung mass (assuming 1000g for humans and 1g for rats). Extrapolation by lung surface area differences (e.g., 143 m^2 human; 0.39 m^2 rat) would provide higher dose estimates by a factor of approximately three. Other factors influencing variability and uncertainty in the dose estimates were not evaluated. Thus, there may be additional sources of uncertainty that are not accounted for in the estimated LCLs.

Table 4-11 compares the lung cancer risk estimates with thresholds (for no effect) extrapolated from the rat pulmonary inflammation data. No uncertainty factors have been applied to these

threshold estimates. NIOSH is presenting these data here as additional support for selection of critical risk estimates.

For fine TiO_2, the BMD model (with linear extrapolation) and the linearized multistage model (i.e., dose predicted directly from the model without linear extrapolation), predict a 1/1000 excess risk of lung cancer at concentrations in the range of 1 to 2 mg/m^3 over a 45-year working lifetime. For ultrafine TiO_2, the BMD and linearized multistage models predict a 1/1000 excess risk of lung cancer in the range of 0.05 to 0.2 mg/m^3 over a 45-year working lifetime. Given the uncertainty in model form and rat data indicating nonlinear dose-response, these linear models may overestimate the risk of lung cancer in humans. The estimated working lifetime exposure concentrations associated with 1/1000 excess risk of lung cancer from the BMA approach (which considers the fit of both linear and nonlinear models to the data) were higher —approximately 5 mg/m^3 (fine TiO_2) and 0.5 mg/m^3 (ultrafine TiO_2). While the BMA approach provides a capability to use all of the information on the various model fits to the data, it is a relatively new approach that has had limited evaluation to date.

To be health protective, NIOSH derived the RELs from the linearized models. The RELs were selected based on the following considerations of the risk estimates (Tables 4-7 and 4-8). As mentioned above, the linearized models predict a 1/1000 excess risk of lung cancer after a 45-year working lifetime exposure to a mean concentration in the range of 1 to 2 mg/m^3 of fine TiO_2; thus, NIOSH determined that it is reasonable and prudent to recommend 1.5 mg/m^3 as the REL for fine TiO_2. This value is also consistent with the previously established MAK value of 1.5 mg/m^3 for fine TiO_2, based on different data and approach (although the MAK value is a

longer-term average value) [DFG 2000]. For ultrafine TiO_2, these linearized models predict a 1/1000 excess risk of lung cancer after a 45-year working lifetime exposure to a mean concentration of 0.05 to 0.2 mg/m^3; thus, NIOSH determined that it is reasonable and prudent to recommend 0.1 mg/m^3 as the REL for ultrafine TiO_2.

The unadjusted (i.e., no uncertainty factors) analyses of pulmonary inflammation data in rats provide similar exposure estimates to those derived from considering 1/1000 excess risk of lung cancer. While there is no *a priori* reason why these estimates would necessarily be similar, this finding suggests that exposures below these concentrations over a working lifetime may be associated with less than 1/1000 excess risk of lung cancer if it occurs via a secondary genotoxic mechanism. However, there is also uncertainty in these risk estimates and in the possible cancer mechanism in humans.

4.5 QUANTITATIVE COMPARISON OF RISK ESTIMATES FROM HUMAN AND ANIMAL DATA

A quantitative comparison was performed of the rat-based MLE excess risk estimates for lung cancer to the 95% UCL of excess risk from the epidemiologic studies (Appendices E and F) to quantitatively compare the rat- and human-based excess risks of lung cancer by using hypothesis tests with results from the human and rat studies. Comparisons were made using several differing assumptions to include alternative plausible approaches. If the sensitivity of the rat response to inhaled particulates differs from that of humans, then the excess risks derived from the rat data would be expected to differ from the excess risks estimated from the human studies. The results of the statistical tests, comparing the rat- and human-based excess risk estimates,

were used to assess whether or not there was adequate precision in the data to reasonably exclude the rat model as a basis for predicting the excess risk of lung cancer in humans exposed to TiO_2.

The results of these comparisons showed that the MLE excess risk estimates from the rat studies were generally lower than the 95% UCL from the human studies for estimated working lifetime (Appendix F, Tables F-1 and F-2). These results indicate, that given the variability in the human studies [Fryzek et al. 2003; Boffetta et al. 2004], the rat-based excess risk estimates cannot reasonably be dismissed from use in predicting the excess risk of lung cancer in humans exposed to TiO_2. Thus, NIOSH determined that it is prudent to use these rat dose-response data for risk assessment in workers exposed to TiO_2.

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Table 4-1. Comparison of rat inhalation studies used to model the relationship between titanium dioxide and pulmonary inflammation

Experimental conditions	Study	
	Tran et al. [1999]	Cullen et al. [2002]
TiO_2 particle size: MMAD (GSD)*	2.1 (2.2) μm	1.2 (2.2 μm)
Specific surface area	6.7 m^2/g	6.41 m^2/g
Rat strain, sex	Male, Wistar rats	Male, Wistar rats
Exposure conditions	Whole body inhalation 7 hr/day, 5 days/week	Nose-only inhalation 6 hr/day, 5 days/week
TiO_2 dose: concentration, duration	25 mg/m^3, 7.5 months 50 mg/m^3, 4 months	140 mg/m^3, 2 months

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1686 *MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation
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Table 4-2. Threshold estimates for particle surface area dose associated with pulmonary inflammation (PMNs* in BAL fluid) in rats, based on piecewise-linear model (m^2)

Data modeled	MLE	95% LCL	95% UCL
TiO_2 [Tran et al. 1999]	0.0134	0.0109	0.0145
TiO_2 [Cullen et al. 2002]	0.0409	0.0395	0.0484

*Abbreviations: BAL fluid = bronchoalveolar lavage; LCL = lower confidence limit; MLE = maximum likelihood estimate; PMNs = polymorphonuclear leukocytes; TiO_2 = titanium dioxide; UCL = upper confidence limit.

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Table 4-3. Estimated mean airborne mass concentrations of fine and ultrafine TiO_2* in humans and related human lung burdens (TiO_2 surface area dose) associated with pulmonary inflammation after a 45-year working lifetime

	Critical dose in human lungs†				Mean airborne exposure‡			
	Particle surface area (m^2/lung)		Particle mass (g/lung)		MPPD (ICRP) lung model (mg/m^3)		Interstitial/ sequestration lung model (mg/m^3)	
Particle size and study	**MLE**	**95% LCL**	**MLE**	**95% LCL**	**MLE**	**95% LCL**	**MLE**	**95% LCL**
Fine TiO_2 (2.1 μm, 2.2 GSD; 6.68 m^2/g):								
Tran et al. [1999]	13.4	10.9	2.0	1.6	1.9	1.5	1.0	0.8
Cullen et al. [2002]	40.9	39	6.1	5.9	5.8	5.6	3.0	2.8
Ultrafine TiO_2 (0.8 μm, 1.8 GSD; 48 m^2/g)§:								
Tran et al. [1999]	13.4	10.9	0.28	0.23	0.22	0.18	0.11	0.09
Cullen et al. [2002]	40.9	39	0.85	0.82	0.66	0.64	0.32	0.30

*Abbreviations: MPPD = multi-path particle deposition [CIIT and RIVM 2002] model, including ICRP [1994] clearance model; GSD = geometric standard deviation; ICRP = International Commission on Radiological Protection; LCL = lower confidence limit; MLE = maximum likelihood estimate; TiO_2 = titanium dioxide.

†MLE and 95% LCL were determined in rats (Table 4-2) and extrapolated to humans based on species differences in lung mass (assuming 1 g in rats and 1,000 g in humans). Particle mass dose was estimated from the particle surface area dose, assuming specified specific surface.

‡Mean concentration estimates derived from the CIIT and RIVM [2002] lung model, which includes the ICRP [1994] clearance model. The interstitial sequestration lung model was derived from coal miner data [Kuempel et al. 2001a,b; Tran and Buchanan 2000].

§Mass median aerodynamic diameter (MMAD). Ultrafine particle size is for agglomerate [Heinrich et al. 1995].

Table 4-4. Summary of chronic inhalation studies in rats exposed to TiO_2*

Particle size and type; study	Rat strain	Mean body weight of controls at 24 months (g)		Mean lung weight of controls at 24 months (g)		Treated rats					
						Particle size MMAD (μm) and specific SA (m^2/g TiO_2)	Exposure concentration (mg/m^3)	Retained mean dose (mg TiO_2/ lung)†		Tumor proportion (rats with tumors / total rats)	
		Female	Male	Female	Male			Female	Male	Female	Male	Average
Fine TiO_2 (≥ 99% rutile):												—
Lee et al. [1985, 1986]	Sprague-Dawley (crl:CD)	557	780	2.35	3.25	MMAD: 1.5 to 1.7 SA: 4.99 [Driscoll 1996]	0 10 50 250	0 32.3 130 545.8	0 20.7 118.3 784.8	0/77 1/75 0/74 26/74	2/79 2/71 1/75 13/77‡	— — —
Muhle et al. [1989, 1991, 1994]; Bellman et al. [1991]	Fischer-344	337	403	1.05	1.38	MMAD: 1.1 (GSD: 1.6) SA: 4.99 (estimate)	0 5	0 2.72		— —	— —	3/100 2/100§
Ultrafine TiO_2 (~80% anatase; ~20% Rutile):												
Heinrich et al. [1995]; Muhle et al. [1994]	Wistar [crl:(WI)BR)]	417	—	1.44		MMAD: 0.80 (GSD: 1.8) (agglomerates) 0.015-0.040 (individual particles) SA: 48 (SD: 2)	0 ~10	0 39.29 (SD: 7.36)		At 24 months: 0/10 (controls) 4/9 (all tumors) At 30 months: 1/217 (controls) 19/100 (no keratinizing cysts)32/100 (all tumors)**		

See footnotes on next page.

*Abbreviations: GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; SA = surface area (mean or assumed mean); SD = arithmetic standard deviation; TiO_2 = titanium dioxide; crl:CD and crl:(WI)BR are the rat strain names from Charles River Laboratories, Inc.

† Lung particle burdens in controls not reported; assumed to be zero.

‡ Tumor types: controls, male: 2 bronchioloalveolar adenomas. At 10 mg/m^3, females: 1 squamous cell carcinoma; males: 1 large cell anaplastic carcinoma and 1 bronchioloalveolar adenoma. At 50 mg/m^3, male: 1 bronchioloalveolar adenoma. At 250 mg/m^3, females: 13 bronchioloalveolar adenomas and 13 squamous cell carcinomas; males: 12 bronchioloalveolar adenomas and 1 squamous cell carcinoma. Of the squamous cell carcinomas, an unknown number were keratinizing cystic squamous cell tumors. Note: It is not clear whether these data are the number of rats with tumors or whether they include multiple tumors in some rats.

§ Dose was averaged for male and female rats because the tumor rates were reported only for male and female rats combined. Tumor types: controls, 2 adenocarcinomas and 1 adenoma. At 5 mg/m^3: 1 adenocarcinoma and 1 adenoma.

** Tumor types: controls, at 30 months: 1 adenocarcinoma. At ~10 mg/m^3: 20 benign squamous-cell tumors, 3 squamous-cell carcinomas, 4 adenomas, and 13 adenocarcinomas (includes 8 rats with 2 tumors each).

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Table 4-5. BMD* and BMDL estimates of TiO_2 particle surface area dose in rat lungs (m^2/g) associated with specified excess risk of lung cancer†

Model: BMDS [EPA 2003]	P(M|D)	*P*-value (for lack of fit)‡	BMD and BMDL by excess risk level					
			1/10§		1/1,000§		1/1,000**	
			BMD	BMDL	BMD	BMDL	BMD	BMDL
Gamma	0.02	0.53	1.04	0.83	0.28	0.042	0.010	0.0083
Logistic	0.30	0.50	1.01	0.92	0.034	0.025	0.010	0.0092
Multistage	0.00	0.61	1.04	0.86	0.22	0.014	0.010	0.0086
Probit	0.26	0.48	0.98	0.88	0.028	0.022	0.0098	0.0088
Quantal-linear	0.03	0.26	0.81	0.62	0.0076	0.0059	0.0081	0.0062
Quantal-quadratic	0.38	0.57	0.96	0.85	0.094	0.083	0.0096	0.0085
Weibull	0.02	0.51	1.05	0.84	0.23	0.035	0.010	0.0084
BMA††	—	—	0.98	0.87	0.062	0.046	0.0097	0.0087

*Abbreviations: BMA = Bayesian modeling averaging; BMD = benchmark dose; BMDL = benchmark dose low (lower confidence limit for the benchmark dose); BMDS = Benchmark Dose Software; P(M|D) = posterior probability of the model given the data; TiO_2 = titanium dioxide.
†Response modeled: lung tumors excluding cystic keratinizing squamous lesions. Male and female data included—from two studies of fine TiO_2 [Lee et al. 1985; Muhle et al. 1991] and one study of ultrafine TiO_2 [Heinrich et al. 1995].
‡Acceptable model fit determined by $P>0.05$.
§Estimated directly from each model (in multistage, 3rd degree polynomial).
**Estimated from linear extrapolation of BMD and BMDL at 1/10 excess risk level.
††*P*-values are not defined in BMA because the degrees of freedom are unknown.

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Table 4-6. Estimated mean airborne mass concentrations of fine and ultrafine TiO_2 in humans and related human lung burdens (TiO_2* surface area dose) associated with 1/1,000 excess risk of lung cancer after a 45-year working lifetime

Particle size and model fit to rat dose-response data for lung tumors§	Critical dose in human lungs†				Mean airborne exposure‡			
	Particle surface area (m^2/lung)		Particle mass (g/lung)		MPPD (ICRP) lung model (mg/m^3)		Interstitial/ sequestration lung model (mg/m^3)	
	MLE	95% LCL	MLE	95% LCL	MLE	95% LCL	MLE	95% LCL
Fine TiO_2 (2.1 μm, 2.2 GSD; 6.68 m^2/g):								
BMD/linear extrapolation	10	8.6	1.5	1.3	1.2	1.1	0.6	0.5
Linearized multistage model	220	14	33	2.1	31	2.0	15	1.0
BMD/BMA††	62	46	9.3	6.9	8.8	6.6	4.2	3.1
Ultrafine TiO_2 (0.8 μm, 1.8 GSD; 48 m^2/g)‡‡:								
BMD/linear extrapolation	10	8.6	0.21	0.18	0.16	0.14	0.07	0.5
Linearized multistage model	220	14	4.6	0.29	3.5	0.22	1.7	0.10
BMD/BMA††	62	46	1.3	0.96	1.0	0.84	0.5	0.42

*Abbreviations: BMA = Bayesian model averaging; BMD = benchmark dose; MPPD = multi-path particle deposition [CIIT and RIVM 2002] model, including ICPR [1994] clearance model;; GSD = geometric standard deviation; ICRP = International Commission on Radiological Protection; LCL = lower confidence limit; MLE = maximum likelihood estimate; TiO_2 = titanium dioxide.

†MLE and 95% LCL were determined in rats (Table 4-5) and extrapolated to humans based on species differences in lung mass (assuming 1 g in rats and 1,000 g in humans). Particle mass dose was estimated from the particle surface area dose, assuming the specified specific surface area.

‡Mean concentration estimates were derived from the CIIT and RIVM [2002] lung model, which includes the ICRP [1994] alveolar model. The interstitial sequestration lung model was derived from coal miner data [Kuempel et al. 2001a,b; Tran and Buchanan 2000].

§Without keratinizing cystic lesions.

**Used linear extrapolation from 10% excess risk from multistage model (most models gave similar estimates for the 1/10 MLE excess risk) (Table 4-5).

††BMA combined estimates from all models (Table 4-5).

‡‡Mass median aerodynamic diameter (MMAD). Agglomerated particle size for ultrafine TiO_2 was used in the deposition model [CIIT and RIVM 2002]. Although individual particle size was not used in the dosimetry model, it is reflected in the specific surface area. Specific surface area was used to convert from particle surface area dose to mass dose; thus airborne particles with different size distribution and specific surface area would result in different mass concentration estimates from those shown here.

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Table 4-7. Excess risk of lung cancer per 1,000 workers exposed to various airborne concentrations of fine TiO_2* over a 45-year working lifetime

Model	Airborne exposure concentration (mg/m³ as 8-hr TWA)									
	0.5		1		2		5		10	
	MLE	UCL	MLE	UCL	MLE	UCL	MLE	UCL	MLE	UCL
BMD multistage / linear extrapolation	0.36	0.42	0.73	**0.83**†	1.46	1.67	3.65	4.17	7.33	8.33
Linearized multistage / model-predicted	3.98×10^{-6}	0.244	0.0000319	0.488	0.000255	**0.975**†	0.00398	2.44	0.0319	4.87
BMD/BMA	0.073	—	0.15	—	0.30	—	**0.80**†	—	1.76	—

*Abbreviations: BMD = benchmark dose; BMA = Bayesian model averaging; MLE = maximum likelihood estimate; TWA = time-weighted average; UCL = 95% upper confidence limit.

† Indicates that the excess risk estimates (UCL or BMA) are near 1/1,000).

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Table 4-8. Excess risk of lung cancer per 1,000 workers after a 45-year working lifetime of exposure to various mean airborne concentrations of ultrafine TiO_2*

	Mean airborne concentration (mg/m^3 as 8-hr TWA)											
	0.05		0.1		0.2		0.5		1		2	
Model	**MLE**	**UCL**	**MLE**	**UCL**	**MLE**	**UCL**	**MLE**	**UCL**	**MLE**	**UCL**	**MLE**	**UCL**
BMD multistage / linear extrapolation	0.83	**1.010**†	1.11	1.35	1.68	2.05	2.97	3.62	5.94	7.23	11.50	13.99
Linearized multistage / model-predicted	2.77×10^{-6}	0.216	2.21×10^{-5}	0.432	0.000160	**0.836**†	0.00277	2.16	0.0221	4.31	0.160	8.36
BMD/BMA	0.184	—	0.249	—	0.384	—	**0.703**†	—	1.53	—	3.43	—

*Abbreviations: BMD = benchmark dose; BMA = Bayesian model averaging; MLE = maximum likelihood estimate; TWA = time-weighted average; UCL = 95% upper confidence limit.
†Indicates that the excess risk estimates (UCL or BMA) are near 1/1,000.

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Table 4-9. Estimated particle surface area dose of fine TiO_2 in workers' lungs after a 45-year working lifetime compared with rat-based thresholds for pulmonary inflammation

	Workers' mean airborne exposure (mg/m^3)				
Item	**0.5**	**1**	**2**	**5**	**10**
Estimated TiO_2 surface area dose:					
Workers' lungs (m^2)	3.5	7.0	14	35	70
Rat equivalent (m^2)	0.0035	0.0070	0.014	0.035	0.070
Rat-based threshold for pulmonary inflammation:					
Exceeds LCL of 0.011 m^2 [Tran et al. 1999]	No	No	Yes	Yes	Yes
Exceeds LCL of 0.039 m^2 [Cullen et al. 2002]	No	No	No	No	Yes

*Abbreviations: LCL = lower confidence limit; TiO_2 = titanium dioxide.

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Table 4-10. Estimated particle surface area dose of ultrafine TiO_2 in workers' lungs after a 45-year working lifetime compared with rat-based thresholds for pulmonary inflammation

Item	Workers' mean airborne exposure (mg/m^3)				
	0.05	**0.1**	**0.5**	**1**	**2**
Estimated TiO_2 surface area dose:					
Workers' lungs (m^2)	3.1	6.2	31	62	120
Rat equivalent (m^2)	0.0031	0.0062	0.031	0.062	0.12
Rat-based threshold for pulmonary inflammation:					
Exceeds LCL of 0.011 m^2 [Tran et al. 1999]	No	No	Yes	Yes	Yes
Exceeds LCL of 0.039 m^2 [Cullen et al. 2002]	No	No	No	Yes	Yes

*Abbreviations: LCL = lower confidence limit, TiO_2 = titanium dioxide.

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Table 4-11. Summary of quantitative risk estimates for workers exposed to fine and ultrafine TiO_2* at various mean airborne concentrations over a 45-year working lifetime

Response	Workers' mean airborne exposure (mg/m^3)†	
	Fine TiO_2	Ultrafine TiO_2
Lung cancer excess risk ≤ 1/1,000‡	1–5	0.05–0.5
Pulmonary inflammation (below estimated threshold)	< 2–10	< 0.5–1.0

Source: Tables 4-7 and 4-10.
*Abbreviations: BMA = Bayesian model averaging; GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; TiO_2 = titanium dioxide; UCL = upper confidence limit.
†Estimates based on particles with the following specific surface area and MMAD: *fine*— 6.68 m^2/g, MMAD 2.1 μm (2.2 GSD); *ultrafine*—48 m^2/g, MMAD (agglomerated) 0.8 μm (1.8 GSD).
‡As 95% UCL or BMA estimate of excess risk.

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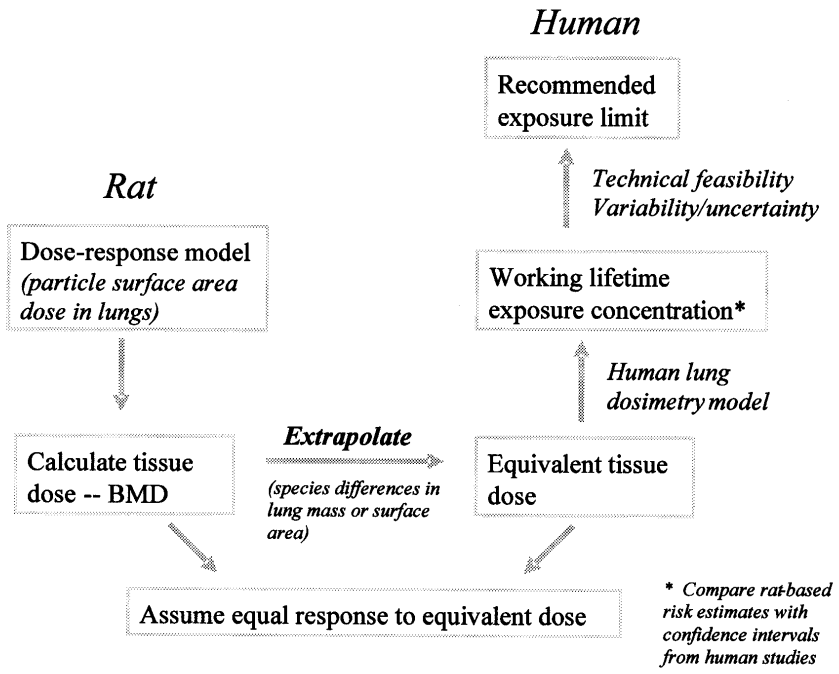


Figure 4-1. Risk assessment approach using rat dose-response data to derive recommended exposure limits for titanium dioxide.

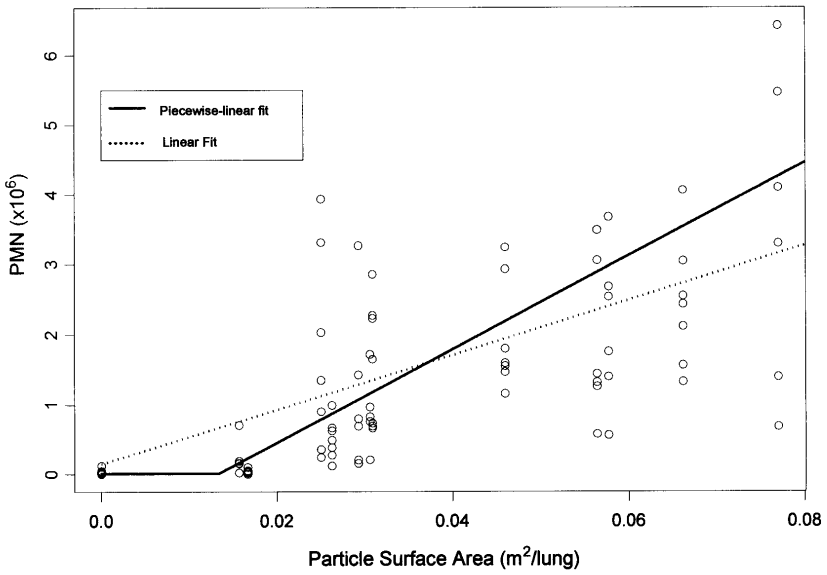
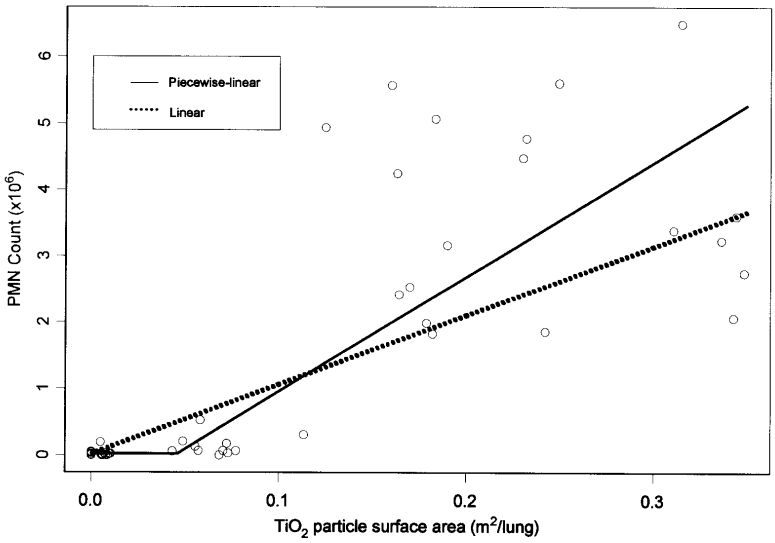


Figure 4-2. Piecewise-linear and linear model fits to rat data on pulmonary inflammation (PMN count) and particle surface area dose of titanium dioxide (data from Tran et al. [1999]).



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1762 **Figure 4-3. Piecewise-linear and linear model fits to rat data on pulmonary inflammation**
1763 **(PMN count) and particle surface area dose of TiO_2 (data from Cullen et al. [2002]).**

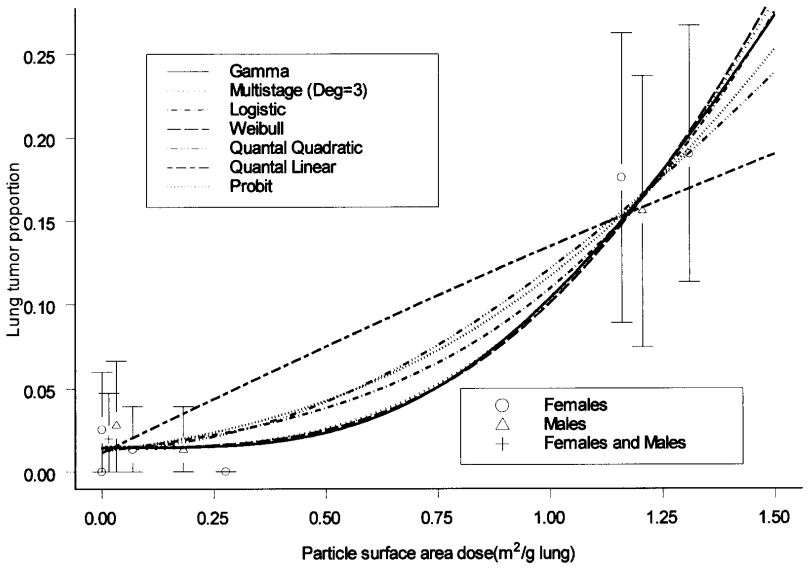

Figure 4-4. BMD models [EPA 2003] fit to the lung tumor data (without squamous cell keratinizing cysts) in male and female rats chronically exposed to fine or ultrafine TiO_2 [Lee et al. 1985; Heinrich et al. 1995] expressed as particle surface area dose. (note: confidence intervals were not constructed when the response proportion was zero).

5. HAZARD CLASSIFICATION AND RECOMMENDED EXPOSURE LIMITS

NIOSH has reviewed the relevant animal and human data for assessing the carcinogenicity of TiO_2 and has reached the following conclusions. First, the tumorigenic effects of TiO_2 exposure in rats appear not to be chemical-specific or a direct action of the chemical substance itself. Rather, these effects appear to be a function of particle size and surface area acting through a secondary genotoxic mechanism associated with persistent inflammation. Second, current evidence indicates that occupational exposures to low concentrations of TiO_2 produce a negligible risk of lung cancer in workers.

On the basis of these findings, NIOSH has determined that insufficient evidence exists to designate TiO_2 as a "potential occupational carcinogen" at this time. NIOSH will reconsider this determination if further relevant evidence is obtained. However, evidence of tumorigenicity in rats at high exposure concentrations warrants the use of prudent health-protective measures for workers until we have a more complete understanding of the possible health risks. Therefore, NIOSH recommends exposure limits of 1.5 mg/m^3 for fine and 0.1 mg/m^3 ultrafine TiO_2 as time-weighted average concentrations for up to 10 hr/day during a 40-year work week. These levels will serve to minimize any risks that might be associated with the development of pulmonary inflammation and cancer.

5.1 HAZARD CLASSIFICATION

NIOSH reviewed the current scientific data on TiO_2 to evaluate the weight of the evidence for the NIOSH designation of TiO_2 as a "potential occupational carcinogen." Two factors were considered in this evaluation: (1) the evidence in humans or animals for an increased risk of lung cancer from inhalation of TiO_2, including exposure up to a full working lifetime, and (2) the evidence on the biologic mechanism of the dose-response relationship observed in rats, including evaluation of the particle characteristics and dose metrics that are related to the pulmonary effects.

No exposure-related increase in carcinogenicity was observed in the epidemiologic studies conducted on workers exposed to TiO_2 dust in the workplace [Boffetta et al. 2001, 2003, 2004; Fryzek et al. 2003; 2004a,b]. In rats exposed to fine TiO_2 by chronic inhalation, lung tumors were elevated at 250 mg/m^3, but not at 10 or 50 mg/m^3 [Lee et al. 1985; 1986a]. In contrast, chronic inhalation exposures to ultrafine TiO_2 at approximately 10 mg/m^3 resulted in a statistically significant increase in malignant lung tumors in rats, although lung tumors in mice were not elevated [Heinrich et al. 1995]. The lung tumors observed in rats after exposure to 250 mg/m^3 were the basis for the original NIOSH designation of TiO_2 as a "potential occupational carcinogen." NIOSH evaluated these dose-response data in humans and animals, along with the mechanistic factors described below, in assessing the scientific basis for the current NIOSH designation of TiO_2 as a "potential occupational carcinogen." In addition, NIOSH used the rat dose-response data in a quantitative risk assessment, to develop estimates of excess risk of nonmalignant and malignant lung responses in workers over a 45-year working lifetime. These

risk estimates were used in the development of recommended exposure limits for fine and ultrafine TiO_2.

5.1.1 Mechanistic Considerations

The mechanistic data considered by NIOSH were obtained from published subchronic and chronic studies in rodents exposed by inhalation to TiO_2 or other poorly soluble low toxicity (PSLT) particles. These studies include findings on the kinetics of particle clearance from the lungs, and on the nature of the relationship between particle surface area and pulmonary inflammation or lung tumor response. The mechanistic issues considered by NIOSH include: the influence of particle size or surface area (vs. specific chemical reactivity) on the carcinogenicity of TiO_2 in rat lungs; the relationship between particle surface area dose and pulmonary inflammation or lung tumor response in rats; and the mechanistic evidence on the development of particle-elicited lung tumors in rats.

The conclusion that inhaled TiO_2 is carcinogenic in rats because of its particulate nature and not due to a chemical-specific reaction is supported by studies on the dose-response relationship to malignant and nonmalignant lung diseases and by mechanistic information on the relationship between particle surface area dose, pulmonary inflammation and its sequela, and lung cancer in the rat lung. The dose-response relationships for TiO_2 and various other PSLT particles can be described using the same dose-response curve when surface area, rather than mass, is used as the dose metric. If the cancer response was due to the chemical compound itself, the potencies of different chemicals would not be expected to be equivalent when plotted as surface area dose. This is illustrated in Figure 3-2, where crystalline silica has a steeper dose-response curve for

pulmonary inflammation, even when dose is expressed as particle surface area, whereas fine TiO_2 (from two studies), ultrafine TiO_2, and fine $BaSO_4$ data all fit the same dose-response curve. Similarly, several types of PSLT particles follow a consistent dose-response relationship for rat lung tumors (Figure 3-4). The importance of particle surface area in the dose-response relationship for lung tumors in the rat is illustrated in Figures 3-3 and 3-5, where the dose-response is similar for fine and ultrafine TiO_2 on a particle surface area basis, but ultrafine TiO_2 is more potent on a mass basis, presumably due to the greater surface area per unit mass. In the rat, the carcinogenic potency on a mass basis was greater for ultrafine TiO_2 than for fine TiO_2 – after chronic inhalation exposure to approximately 10 mg/m^3 of ultrafine TiO_2, 19% of female rats developed lung tumors (adenocarcinoma, squamous cell carcinoma, and adenoma), while male and female rats exposed to fine TiO_2 had no excess of lung tumors at either 10 or 50 mg/m^3, and at 250 mg/m^3 approximately 17% developed adenomas [Lee et al. 1985; Heinrich et al. 1995].

Mechanistic studies of inhaled TiO_2 support a plausible sequence of events via a secondary genotoxic mechanism. Specifically, a nonlinear relationship has been observed between the particulate surface area dose of TiO_2 and the number of polymorphonuclear leukocyte (PMN) cells in the lungs, a marker for pulmonary inflammation [Oberdörster et al. 1992; Tran et al. 1999]. Persistent pulmonary inflammation has been shown to generate reactive oxygen and nitrogen species, which if unquenched by antioxidant defenses, can eventually cause oxidative stress, tissue damage, and epithelial cell proliferation and hyperplasia, followed by the development of nonmalignant and malignant lung tumors in rats [Oberdörster 1995, 1996; Mossman 2000]. These effects increase significantly when the particle clearance processes in

the rat lungs are overwhelmed, leading to greater retention of particles in the lungs (called rat lung overload) [ILSI 2000].

Ultrafine TiO_2 was shown to have greater free radical activity than fine TiO_2, and also caused much greater damage to supercoiled plasmid DNA—an effect that was reduced by mannitol, indicating involvement of hydroxyl radicals. Moreover, particle-elicited PMN cells (neutrophils) and alveolar macrophages were shown to induce a specific gene mutation (hprt) in the lung epithelial cells of rats exposed to TiO_2 and other particles, and these mutations were inhibited in vitro by the addition of the antioxidant catalase [Driscoll et al. 1997]. These studies provide mechanistic evidence for the role of persistent neutrophilic inflammation and cell-derived oxidants in the rat lung tumor response to particles in the lungs. These mechanistic factors are also consistent with the observed nonlinear dose-response relationships in rats inhaling TiO_2.

NIOSH has considered these dose-response and mechanistic data and concludes that a plausible interpretation of the scientific evidence is that TiO_2 is a carcinogen in rat lungs via a non-chemical specific, secondary genotoxic mechanism involving persistent pulmonary inflammation.

5.1.2 Cancer Classification in Humans

The lack of an exposure-response relationship in the epidemiologic studies of workers exposed to TiO_2 dust in the workplace should not be interpreted as clear evidence of a discordance between the mechanism presumed to operate in rats and the human potential for carcinogenicity. As demonstrated by the quantitative comparison between the animal and human studies (Section

3.5), the responses were not statistically inconsistent: the epidemiologic studies had insufficient power to replicate or refute the animal dose-response.

However, the mechanistic data reviewed above leave open the possibility of species differences beyond what would be anticipated for a genotoxic carcinogen. Although it is plausible that the secondary genotoxic mechanism described above operates in humans exposed to TiO_2 dust, there is insufficient evidence to corroborate this. In addition, there is limited information on the kinetics or specific physiological response to TiO_2 particles in humans. Because of this lack of information, it is not possible to determine whether or not exposures to high concentrations of TiO_2 are carcinogenic in humans, as they are in rats. The evidence suggests that exposures with insufficient TiO_2 surface area are not likely to show carcinogenic activity in any test species, and the current epidemiologic data provide insufficient indication of carcinogenicity in humans. NIOSH interprets this information to indicate that occupational exposures to low concentrations of TiO_2 pose a negligible risk of cancer in workers. For this reason, NIOSH has removed the classification of TiO_2 as a potential occupational carcinogen, with the recommendation that occupational exposures to TiO_2 should be controlled to levels that are unlikely to cause persistent inflammation and thus initiate a secondary genotoxic response. The RELs were developed using the rat dose-response data, including the lung tumor data, to provide health-protective recommendations for workers exposed to fine or ultrafine TiO_2. NIOSH will reconsider the cancer classification if sufficient additional scientific evidence becomes available.

5.1.3 Basing the RELs on Rat Tumor Data

NIOSH concluded from reviewing the mechanistic evidence that TiO_2 is carcinogenic in rats because of its physical properties as a particulate, which at sufficiently high surface area doses causes persistent pulmonary inflammation and lung tumors. The evidence indicates this occurs through a secondary genotoxic mechanism, rather than to any inherent carcinogenicity of the chemical TiO_2. Although there is little direct evidence that this mechanism operates in humans (leading NIOSH to remove the designation, "potential occupational carcinogen"), there is also no compelling evidence to refute the plausibility of this mechanism in humans. Therefore, NIOSH has determined that the rat is a reasonable model to predict human risks and has used the rat tumor-response data supported by the inflammation data as the basis for the recommended exposure limits (RELs). NIOSH believes that this reflects both the weight of evidence for the potential human carcinogenicity of TiO_2 and NIOSH's concern that the RELs be sufficiently protective of human health.

NIOSH has considered the evidence suggesting that rats may be an inappropriate model for human lung cancer after exposure to particulates and has concluded that the rat is a reasonable model for predicting human lung cancer risks. Although there is not extensive evidence that the overloading of lung clearance, as observed in rats (Chapter 3), occurs in humans, lung burdens consistent with overloading doses in rats have been observed in some humans with dusty jobs (e.g., coal miners) [Stöber et al. 1965; Carlberg et al. 1971; Douglas et al. 1986]. Rather than excluding the rat as the appropriate model, the lung overload process may cause the rat to attain lung burdens comparable to those that can occur in workers with dusty jobs. In addition, evidence suggests that, as in the rat, inhalation of particles increases the human inflammatory

response, and increases in the inflammatory response may increase the risk of cancer (see Section 3.5.2). This information provides additional support for the determination that the rat is a reasonable animal model with which to predict human tumor response for other particles, such as TiO_2.

Examination of the lung cancer dose-response curve for TiO_2 and some PSLT particles shows a nonlinearity in response. For example, the best fit in the multistage model was a cubic model with no linear term. This is consistent with the proposed mechanism of action of TiO_2 in the rat: as inhaled particles accumulate in the lungs and a critical dose is reached, pulmonary inflammation increases sharply, accompanied by cellular proliferation and eventually carcinogenesis by a secondary genotoxic mechanism involving reactive oxygen species produced during inflammation. The RELs for TiO_2 are based on the linearized upper bound on risk from the multistage model, which is expected to be health-protective due to the nonlinearity in the dose-response curve. The nonlinear shape of the maximum likelihood estimate of the cancer response increases confidence that the true risks of cancer are lower than 1/1000 at the RELs and could be as low as zero. This is also consistent with removal of the designation, "potential occupational carcinogen" from TiO_2.

5.2 RECOMMENDED EXPOSURE LIMITS

NIOSH recommends exposure limits of 1.5 mg/m^3 for fine TiO_2 and 0.1 mg/m^3 for ultrafine TiO_2 as time-weighted average concentrations (TWA) for up to 10 hr/day during a 40-hour work week, using the international definitions of respirable dust [CEN 1993; ISO 1995] and the NIOSH Method 0600 for sampling airborne respirable particles [NIOSH 1998]. NIOSH selected

these exposure limits for recommendation because they would reduce working lifetime risks for lung cancer to below 1/1000 even under the worst-case assumption of low-dose linearity in the exposure-response relationship. NIOSH believes that the true risk of lung cancer due to exposure to TiO_2 at these concentrations is much lower than 1/1000, and could in fact be zero. To account for the risk that exists in work environments where airborne exposures to fine and ultrafine TiO_2 occur, exposure measurements to each size fraction should be combined using the additive formula and compared to the additive REL of 1 (unitless) (see Figure 6.1 Exposure assessment protocol for TiO_2).

"Respirable" is defined as particles of aerodynamic size that, when inhaled, are capable of depositing in the gas-exchange (alveolar) region of the lungs [ICRP 1994]. Sampling methods have been developed to estimate the airborne mass concentration of respirable particles [CEN 1993; ISO 1995; NIOSH 1998]. "Fine" is defined in this document as all particle sizes that are collected by respirable particle sampling (i.e., 50% collection efficiency for particles of 4 μm, with some collection of particles up to10 μm). "Ultrafine" is defined as the fraction of respirable particles with primary particle diameter <0.1 μm, which is a widely used definition. Additional methods are needed to determine whether an airborne respirable particle sample includes ultrafine TiO_2 (Chapter 6).

The separate RELs for fine and ultrafine TiO_2 are supported by the higher lung cancer potency in rats of ultrafine TiO_2 compared to fine TiO_2, which was associated with the greater surface area of ultrafine particles for a given mass. In rats chronically exposed to airborne fine TiO_2,

statistically-significant excess lung tumors were observed only in the 250 mg/m^3 dose group. With chronic exposure to airborne ultrafine TiO_2, lung tumors were seen in rats exposed to an average of approximately 10 mg/m^3.

It may be a better reflection of the entire body of available data to set RELs as the inhaled surface area of the particles rather than the mass of the particles. This would be consistent with the scientific evidence showing an increase in potency with increase in particle surface area (or decrease in particle size) of TiO_2 and other PSLT particles. However, current technology does not permit the routine measurement of the surface area of airborne particles, and dosimetry models would have to be modified to incorporate such data in order to reanalyze the risks to reflect those measurements. Therefore, NIOSH recommends sampling the mass airborne concentration of TiO_2, as two broad primary particle size categories: fine (<10 μm) and ultrafine (< 0.1 μm). These categories reflect current aerosol size conventions, although it is recognized that actual particle size distributions in the workplace will vary. Because agglomerated ultrafine particles are frequently measured as fine-sized but behave biologically as ultrafine particles due to the surface area of the constituent particles, exposures to agglomerated ultrafine particles should be controlled to the ultrafine REL.

The NIOSH REL for fine TiO_2 of 1.5 mg/m^3 is based on an assessment of the lung tumor response in the rat and supported by consideration of the other pulmonary effects of TiO_2. The NIOSH REL for ultrafine TiO_2 of 0.1 mg/m^3 reflects NIOSH's greater concern for the potential carcinogenicity of ultrafine TiO_2 particles. As particle size decreases, the surface area increases (for equal mass), and the tumor potency increases per mass unit of dose. The ultrafine REL is

based on an evaluation of the rat lung cancer data for TiO_2 and supported by the lower critical lung doses for inflammation in the rat. Exposures to workers should be kept as low as feasible and should not exceed the RELs. Interim recommendations for sampling and control of exposures to fine and ultrafine TiO_2 in the workplace are described in Chapter 6.

In the *NIOSH Pocket Guide*, NIOSH will delete the designation "potential occupational carcinogen" and add the following explanatory footnotes to the TiO_2 entry:

> *TiO_2 particles may be found as pigment-grade or fine TiO_2 (<10 μm) or ultrafine (<0.1 μm) (primary particle sizes). The carcinogenicity of TiO_2 is believed to be related to a nonchemical-specific interaction of the particles with lung tissue, causing chronic inflammation and eventually tumors in rat lungs. This effect is related to the surface area of the particle, which increases as the particle size decreases. For that reason, NIOSH has much greater concern for the carcinogenicity of ultrafine TiO_2, and has set the REL for ultrafine TiO_2 much lower than that for fine TiO_2. The REL for ultrafine TiO_2 also applies to agglomerated ultrafine TiO_2 particles, even when the agglomerate is greater than 0.1 μm in diameter.*

6. MEASUREMENT AND CONTROL OF TiO_2 AEROSOL IN THE WORKPLACE

6.1 EXPOSURE METRIC

Based on the observed relationship between particle surface area dose and toxicity (Chapters 3 and 4), the measurement of aerosol surface area would be the preferred method for evaluating workplace exposures to TiO_2. However, personal sampling devices that can be routinely used in the workplace for measuring particle surface area are not currently available. As an alternative, if the airborne particle size distribution of the aerosol is known in the workplace and the size distribution remains relatively constant with time, mass concentration measurements may be useful as a surrogate for surface area measurements. NIOSH is recommending that a mass-based airborne concentration measurement be used for monitoring workplace exposures to fine and ultrafine TiO_2 until more appropriate measurement techniques can be developed. NIOSH is currently evaluating the efficacy of various sampling techniques for measuring fine and ultrafine TiO_2 and may make specific recommendations at a later date.

In the interim, personal exposure concentrations to fine (pigment-grade) and ultrafine TiO_2 should be determined with NIOSH Method 0600 using a standard 10-mm nylon cyclone or equivalent particle size-selective sampler [NIOSH 1998]. Measurement results from NIOSH Method 0600 should provide a reasonable estimate of the exposure concentration to fine and ultrafine TiO_2 at the NIOSH RELs of 1.5 and 0.1 mg/m^3, respectively, when the predominant exposure to workers is TiO_2. No personal sampling devices are available at this time to

specifically measure the mass concentrations of ultrafine aerosols; however, the use of NIOSH Method 0600 will permit the collection of most airborne ultrafine particles and agglomerates.

In work environments where exposure to other types of aerosols occur or when the size distribution of TiO_2 (fine versus ultrafine) is unknown, other analytical techniques may be needed to characterize exposures. NIOSH Method 7300 [NIOSH 2003] can be used to assist in differentiating TiO_2 from other aerosols collected on the filter while electron microscopy, equipped with an energy dispersive x-ray analyzer (EDXA), may be needed to identify and measure the fraction of the mass concentration that is attributable to fine and ultrafine TiO_2 particles. In workplaces where TiO_2 is purchased as a single type of bulk powder, the primary particle size of the bulk powder can be used to determine whether the REL for fine or ultrafine should be applied when adequate airborne exposure data exist to confirm that the airborne particle size has not substantially been altered during the handling and/or material processing of TiO_2.

6.2 EXPOSURE ASSESSMENT

A multi-tiered workplace exposure assessment might be warranted in work environments where the airborne particle size distribution of TiO_2 is unknown (fine versus ultrafine) and/or where other airborne aerosols may interfere with the interpretation of sample results. Figure 6-1 illustrates an exposure assessment strategy that can be used to ascertain the airborne size distribution of TiO_2 so that appropriate exposure concentrations can be determined for fine and ultrafine TiO_2. An initial assessment of the workplace should include the simultaneous collection of a respirable dust sample as described in NIOSH Method 0600 with the collection of

a respirable dust sample using a mixed cellulose ester filter (MCEF).* If the respirable exposure concentration for TiO_2 (as determined by Method 0600) is less than 0.1 mg/m^3 then no further action is required; however, subsequent workplace sampling should be performed at specified time intervals and when a process change occurs to ensure that exposures remain below the REL. If the exposure concentration exceeds 0.1 mg/m^3, then additional characterization of the sample is needed to determine the percentage and particle size distribution of TiO_2 so that the appropriate comparison can be made with the fine and ultrafine TiO_2 RELs. To assist in this assessment, the duplicate respirable sample collected on a MCEF should be evaluated using transmission electron microscopy (TEM) to size particles and determine the percentage of TiO_2 for particles greater than and less than 0.1 µm in diameter. The identification of TiO_2 can be accomplished using a TEM equipped with an energy dispersive x-ray analyzer (EDXA). Once the percent of TiO_2 (by particle size) has been determined, adjustments can be made to the mass concentration (determined by Method 0600) to assess whether exposure to the NIOSH RELs for fine, ultrafine, or combined fine and ultrafine TiO_2 had been exceeded. To minimize the need for the systematic collection of respirable samples for TEM analysis, samples collected for respirable TiO_2 using Method 0600 should also be routinely analyzed by inductively coupled argon plasma (ICP) spectroscopy for titanium using NIOSH Method 7300. The results obtained using Method 7300 should be compared with the respirable mass concentration measurements to determine the relative percentage of TiO_2 in the concentration measurements. The routine determination of TiO_2 (using Method 7300) from samples collected and analyzed by Method

* Note: The collection time for samples using a MCEF may need to be shorter than the duplicate samples collected and analyzed by Method 0600 to ensure that particle loading on the filter doesn't become excessive and hinder particle sizing and identification by TEM.

0600 can provide some quality assurance that the percent of airborne TiO_2 does not change over time.

6.3 CONTROL OF WORKPLACE EXPOSURES TO TiO_2

Given the extensive commercial use of fine (pigment grade) TiO_2, the potential for occupational exposure exists in many workplaces. However, few data exist on airborne concentrations and sources of exposure. Most of the available data for fine TiO_2 are reported as total dust and not as the respirable fraction. Historical total dust exposure measurements found in TiO_2 production plants often exceeded 10 mg/m^3 [IARC 1989] while more contemporary measurement data indicate that mean total dust measurements in these plants may be below 3 mg/m^3 (1.1 mg/m^3 median) [Fryzek et al. 2003]. Few data exist to quantify exposures to fine TiO_2 during its handling and use. Given the particle size dimensions of fine TiO_2 (~0.1 μm to 4 μm, avg. of 0.5 μm) [Malvern Instruments 2004], it is reasonable to conclude that a significant fraction of total dust measurements reported for TiO_2 are comprised of respirable particles. Although NIOSH is not aware of any extensive commercial production of ultrafine anatase TiO_2 in the United States, it may be imported for use in the United States. Likewise, fine rutile TiO_2 may be micronized to produce an ultrafine particle fraction for product applications such as cosmetics. No data have been published on occupational exposures to ultrafine TiO_2.

Although limited data exist on occupational exposures to TiO_2, reducing exposures can be achieved using a variety of standard control techniques [Raterman 1996; Burton 1997]. Standard industrial hygiene practices for controlling airborne hazards include engineering controls, work practices and administrative procedures, and personal protective equipment. Examples of

engineering controls include process modifications and the use of an industrial ventilation system to reduce worker exposures [ACGIH 2001c]. In general, control techniques such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems are the preferred methods for preventing worker exposure to TiO_2. In light of current scientific knowledge regarding the generation, transport, and capture of aerosols, these control techniques should be effective for both fine and ultrafine particles [Seinfeld and Pandis 1998; Hinds 1999]. Conventional engineering controls using ventilation systems to isolate the exposure source from workers should be effective in reducing airborne exposures to fine and ultrafine TiO_2, based on what is known about the motion and behavior of respirable aerosols in the air. Ventilation systems equipped with high efficiency particulate air (HEPA) filters are designed to remove 99.97% of particles 300 nm in diameter. Particles smaller than 200 nm are generally collected on the filter by diffusion, irrespective of the filter pore size. For particles larger than 800 nm, particles are deposited through impaction and interception [Lee and Liu 1981, 1982]. Ventilation systems must be properly designed, tested, and routinely maintained to provide maximum efficiency.

The control of exposures should be primarily accomplished through the use of engineering controls. When engineering controls and work practices cannot reduce worker TiO_2 exposures to below the REL then a respirator program should be implemented. The OSHA respiratory protection standard (29 CFR 1910.134) sets out the elements for both voluntary and required respirator use. All elements of the standard should be followed. Primary elements of the OSHA respiratory protection standard include (1) an evaluation of the worker's ability to perform the work while wearing a respirator, (2) regular training of personnel, (3) periodic environmental monitoring, (4) respirator fit-testing, and (5) respirator maintenance, inspection, cleaning, and

storage. The program should be evaluated regularly by the employer. Respirators should be selected by the person who is in charge of the program and knowledgeable about the workplace and the limitations associated with each type of respirator.

NIOSH provides guidance for selecting an appropriate respirator in the NIOSH Respirator Selection Logic 2004 available online at: http://www.cdc.gov/niosh/docs/2005-100/default.html. The selection logic takes into account the expected exposure concentration, other potential exposures, and the job task. For most job tasks involving only TiO_2 exposure a properly fit-tested half-facepiece particulate respirator will provide protection up to 10 times the respective REL. When selecting the appropriate filter and determining filter change schedules, the respirator program manager should consider that overloading of the filters with particulates may occur because of the size and characteristics of TiO_2 particles.

Employers should establish a risk management program that includes all workers with potential exposure to TiO_2. An important objective of the program should be educating workers about the potential adverse health effects associated with TiO_2 exposure and training them in the safe handling of bulk TiO_2 and TiO_2–products.

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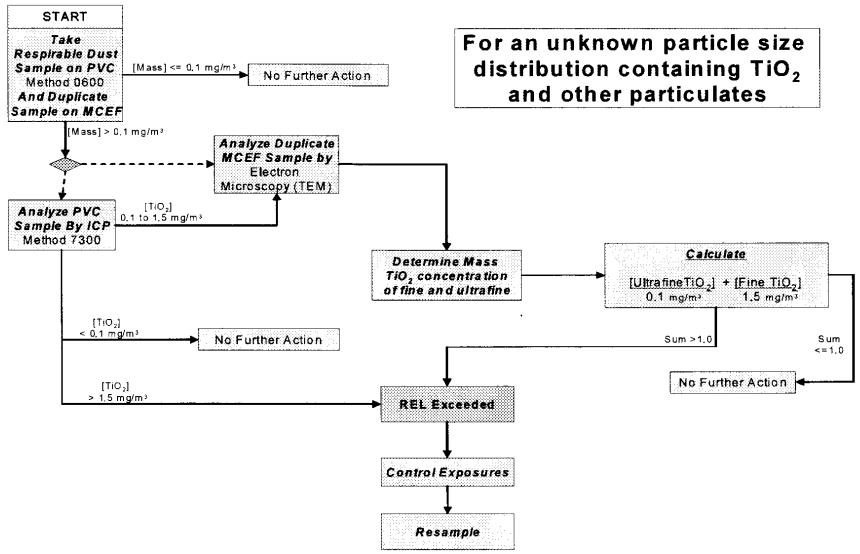

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Figure 6-1. Exposure assessment protocol for TiO_2.

7. RESEARCH NEEDS

Additional data and information are needed to assist NIOSH in evaluating the occupational safety and health issues of working with fine and ultrafine TiO_2. Data are particularly needed on the airborne particle size distributions and exposures to ultrafines in specific operations or tasks. These data may be merged with existing epidemiologic data to determine if exposure to ultrafine TiO_2 is associated with adverse health effects. Information is needed about whether respiratory health (e.g., lung function) is affected in workers exposed to TiO_2. Experimental studies on the mechanism of toxicity and tumorigenicity of ultrafine TiO_2 would increase understanding of whether factors in addition to surface area may be important. Although sampling devices for all particle sizes are available for research purposes, practical devices for routine sampling in the workplace are needed.

7.1 WORKPLACE EXPOSURES AND HUMAN HEALTH

- Quantify the airborne particle size distribution of TiO_2 by job or process, and obtain quantitative estimates of workers' exposures to fine and ultrafine TiO_2.

- Conduct epidemiologic studies of workers manufacturing or using TiO_2-containing products, using quantitative estimates of exposure by particle size, including fine and ultrafine fractions (see bullet above).

- Evaluate the extent to which the specific surface area in bulk TiO_2 is representative of the specific surface area of the airborne TiO_2 particles that workers inhale and that are retained in the lungs.

- Investigate the adequacy of current mass-based human lung dosimetry models for predicting the clearance and retention of inhaled ultrafine particles.

7.2 EXPERIMENTAL STUDIES

- Investigate the fate of ultrafine particles (e.g., TiO_2) in the lungs, and the associated pulmonary responses.

- Investigate the ability of ultrafine particles (e.g., TiO_2) to enter cells and interact with organelle structures and DNA in mitochondria or the nucleus.

7.3 MEASUREMENT, CONTROLS, AND RESPIRATORS

- Develop accurate, practical sampling devices for ultrafine particles (e.g., surface area sampling devices).

- Evaluate effectiveness of engineering controls for controlling exposures to fine and ultrafine TiO_2.

- Initial laboratory research indicates that a properly fit-tested particulate respirator should provide the expected level of protection at the assigned protection factor; however, additional

research is needed to determine whether the appropriate level of protection is being afforded by the respirator during use in the workplace.

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APPENDIX A

MODIFIED LOGISTIC REGRESSION MODEL FOR QUANTAL RESPONSE IN RATS

A modified logistic regression model was constructed to use all tumor data (including squamous cell keratinizing cystic tumors) to account for heterogeneity in tumor response observed between male and female rats in the Lee et al. [1985] and Heinrich et al. [1995] studies. In addition, the Muhle et al. [1991] study reported tumor response for males and females combined. For these reasons, the standard models in the BMDS [EPA 2003] could not be used. The BMDS models do not allow for covariates (e.g., sex) or for alternative model structures to account for the combined data.

In the modified logistic regression model, the total tumor count was evaluated as the sum of tumors from two distinct binomial responses. This implies that the expected response can be modeled as

$$N_{obs} = n_m p_m + n_f p_f \qquad \text{(equation 1)}$$

where $N = n_m + n_f$, and the set (p_m p_f) are binomial probabilities of tumor response for males and females that are modeled using the same assumptions of logistic regression. For example female rats would have the following response:

$$p_f = \frac{\exp(\alpha_f + \beta_f \cdot dose)}{1 + \exp(\alpha_f + \beta_f \cdot dose)} \qquad \text{(equation 2)}$$

that is the same as a logistic model that investigates only female rats. Thus, to model responses across studies using male, female, and male/female combinations, equations (1) and (2) can be used when n_m and n_f are known. When they are not known (using results reported in Muhle et al. [1991]), these quantities are estimated to be $n/2$.

With p_m and p_f now estimable using all data, the benchmark dose (BMD) can be computed by methods described by Gaylor et al. [1998]. Further the benchmark dose lower bound (BMDL) can be computed using profile likelihoods, which are described by Crump and Howe [1985]. For simplicity in the calculation, we compute the male and female BMDL at the nominal level of $\alpha = 0.025$, which implies a combined nominal coverage $\alpha = 0.05$.

APPENDIX B

PIECEWISE LINEAR MODEL FOR PULMONARY INFLAMMATION IN RATS

In modeling pulmonary inflammation (as neutrophilic cell count in BAL fluid) in rat lungs, the response was assumed to be normally distributed with the mean response being a function of dose and the variance proportional to a power of the mean. Thus for the i^{th} rat given the dose d_i the mean neutrophilic cell count would be $\mu_{pmn}(d_i)$ with variance $\alpha(\mu_{pmn}(d_i))^{\rho}$, where μ_{pmn} is any continuous function of dose, α is a proportionality constant, and ρ represents a constant power. The mean response was modeled using a variety of functions of dose; these functions were then used to estimate the critical dose at which the mean neutrophil levels went above the background. For the continuous functions that did not include a threshold parameter, this critical level was found using the BMD method [Crump 1984] and software [EPA 2003]. For purposes of calculation, the BMD was defined as the particle surface area dose in the lungs associated with $\mu_{pmn}(d_i)$ corresponding to the upper 5th percentile of the distribution of PMN counts in control rat lungs.

For the piecewise linear model, which is a threshold model, we assumed no dose-response, and thus no additional risk, above background prior to some critical threshold γ. For points beyond the threshold, the dose-response was modeled using a linear function of dose e.g.:

$$\mu_{pmn}(d_i) = \begin{cases} \beta_0 & d_i < \gamma \\ \beta_0 + \beta_1(d_i - \gamma) & d_i \geq \gamma \end{cases}$$

As the parameter γ is an unknown term, the above function is nonlinear and is fit using maximum likelihood (ML) estimation. Very approximate $(1-\alpha)$% CIs can be found using profile likelihoods [Hudson 1966]. As the confidence limits are only rough approximations, the limits and significance of the threshold can be cross validated using parametric bootstrap methods [Efron and Tibshirani 1998].

APPENDIX C

STATISTICAL TESTS OF THE RAT LUNG TUMOR MODELS

As seen in Figures 3-3 and 3-4, particle surface area dose is a much better dose metric than particle mass dose for predicting lung tumor response in rats. The statistical fit of these models is shown in Table C-1, using either mass or particle surface area dose. These goodness of fit tests show that particle surface area dose provides an adequate fit to models using either the all tumor response or tumors excluding squamous cell keratinizing cysts, and that particle mass dose provides an inadequate fit to these data. The *P*-values are for statistical tests of the lack of fit; thus, $P<0.05$ indicates lack of fit.

Because of the observed differences in tumor response in males and females, when squamous cell keratinizing cystic tumors were included in the analysis (Table 4-4), it was important to test for heterogeneity in response by rat sex. Since the data were from different studies and rat strains, these factors were also investigated for heterogeneity (the influence of study and strain could not be evaluated separately because a different strain was used in each study). Finally, the possibility of heterogeneity in response to fine and ultrafine TiO_2 after adjustment for particle surface area was investigated to determine whether other factors may be associated with particle size that influence lung tumor response and that may not have been accounted for by particle surface area dose. Table C-2 shows that there was statistically significant heterogeneity between male and female rats for the *all lung tumors* response but not for the tumors excluding squamous cell keratinizing cysts. No heterogeneity in tumor response was observed across study/strain or for fine versus ultrafine, when dose was expressed as particle surface area. Therefore, it was

necessary to adjust only for rat sex in the model for all lung tumor response (by including rat sex as a covariate in that model, as well as an adjustment for the combined male/female lung tumor response data in the Muhle et al. [1991] study; see Appendix A).

Table C-1. Goodness of fit of logistic regression models to pooled rat data of lung tumor proportion and titanium dioxide dose (as retained particle mass or surface area in the lungs) in rats after 24-month exposure*

Dose metric	Tumor response	Degrees of Freedom	*P*-value (dose only model)	Degrees of Freedom	*P*-value (dose & sex terms)
Surface area (m^2/g lung)	All tumors	10	0.056	8	0.29
Mass (mg/g lung)		10	<0.0001	8	<0.0001
Surface area (m^2/g lung)	No keratinizing cysts	10	0.50	8	0.62
Mass (mg/g lung)		10	<0.0001	8	<0.0001

* Pearson test for lack of fit. In the model with both dose and sex terms, the slopes and intercepts are averaged for the male/female combined average data from Muhle et al. [1991]. Rat data are from two studies of fine TiO_2 [Lee et al. 1985; Muhle et al. 1991] and one study of ultrafine TiO_2 [Heinrich et al. 1995] (12 data points total).

Table C-2. Tests for heterogeneity of rat sex or study/strain in dose-response relationship, based on likelihood ratio tests

Test [a]	Tumor response	Degrees of Freedom	*P*-value	Heterogeneity
Rat sex (male vs. female) [b,c]	All lung tumors	2	0.012	Yes
	No keratinizing cysts	2	0.14	No
Study/strain [b,d]	All lung tumors	4	0.46	No
	No keratinizing cysts	4	0.44	No
Ultrafine vs. fine (in females) [e,f]	All lung tumors	2	0.66	No
	No keratinizing cysts	2	0.22	No

[a] Null model includes two terms: intercept and slope x surface area dose (m^2/g lung).
[b] Data include Lee et al. [1985] (male, female); Heinrich et al. [1995] (female); and Muhle et al. [1991] (male-female average)—12 data points total.
[c] Full model includes four terms: separate intercepts and slopes for male and female rats (male-female average data was included assigned a value of 0.5 each for male and female indicators).
[d] Full model includes six terms: intercept and slope from null model (for comparison group), and separate intercept and slope terms for each of the other two study/strains.
[e] Data include females from Lee et al. [1985] and Heinrich et al. [1995]—6 data points total.
[f] Full model includes four terms: intercept and slope from null model (for comparison group), and separate intercept and slope terms for the other group.

APPENDIX D

ADDITIONAL MODELING OF RAT LUNG TUMOR DATA

As described in Chapter 4, male and female rat data could be combined for the models of lung tumors without the keratinizing cystic tumors; however, due to heterogeneity by rat sex for the *all lung tumor* response, the BMDS models [EPA 2003] were fit separately to the male and female rat data. The results of these analyses are provided in Table D-1. In addition, a logistic model was developed to account for the differences in the male and female response for all tumors (i.e., including the squamous cell keratinizing cystic tumors); this modified logistic model allowed all of the data to be used in the one overall model. The estimates from the logistic model are provided in Table D-2.

Table D-1. *All tumors*: Benchmark dose (BMD) and lower 95% confidence limit (BMDL) estimates—expressed as titanium dioxide (TiO_2) particle surface area in the lungs (m^2/g)—by model fit separately to male and female rat data.

Model (BMDS 2003)	MALE rats [Lee et al. 1985]				FEMALE rats [Lee et al. 1985; Heinrich et al. 1995]			
	P-value (for lack of fit)	BMD (BMDL) by Excess Risk Level			*P*-value (for lack of fit)	BMD (BMDL) by Excess Risk Level		
		1/10 [a]	1/1000 [a]	1/1000 [b]		1/10 [a]	1/1000 [a]	1/1000 [b]
Gamma	0.51	1.11	0.54	0.011	0.20	0.76	0.20	0.0076
		(0.65)	(0.0062)	(0.0065)		(0.54)	(0.038)	(0.0054)
Logistic	0.64	1.00	0.026	0.01	0.15	0.86	0.050	0.0086
		(0.82)	(0.018)	(0.0082)		(0.77)	(0.027)	(0.0077)
Multistage	0.80	1.05	0.22	0.010	0.30	0.65	0.063	0.0065
		(0.65)	(0.0062)	(0.0065)		(0.51)	(0.0080)	(0.0051)
Probit	0.62	0.98	0.023	0.0098	0.24	0.79	0.044	0.0079
		(0.78)	(0.015)	(0.0078)		(0.70)	(0.023)	(0.0070)
Quantal-linear	0.40	0.87	0.0083	0.0087	0.068	0.37	0.0035	0.0037
		(0.54)	(0.0051)	(0.0054)		(0.30)	(0.0028)	(0.0030)
Quantal-quadratic	0.73	0.98	0.096	0.0098	0.30	0.65	0.063	0.0065
		(0.78)	(0.076)	(0.0078)		(0.58)	(0.057)	(0.0058)
Weibull	0.52	1.15	0.66	0.012	0.16	0.76	0.13	0.0076
		(0.65)	(0.0027)	(0.0065)		(0.52)	(0.024)	(0.0052)
Bayesian Model Average [c]	--	0.96	0.064	0.0096	--	0.74	0.059	0.0074
		(0.75)	(0.032)	(0.0075)		(0.66)	(0.036)	(0.0066)

Footnotes for Table D-1:

[a] Estimated directly from each model (in multistage, degree of polynomial: 3rd, male; 2nd, female).

[b] Estimated from linear extrapolation of BMD and BMDL at 1/10 excess risk level.

[c] *P*-values are not defined in Bayesian model averaging because the degrees of freedom are unknown.

Table D-2. All tumors or lung tumors excluding cystic keratinizing squamous lesions: Logistic (sex-adjusted) model used to estimate benchmark dose (BMD) and lower 95% confidence limit (BMDL) estimates -- expressed as titanium dioxide (TiO_2) particle surface area in the lungs (m^2/g) – in pooled rat data (males, female, and male-female average). [a]

Rat sex	DF	*P*-value (for lack of fit)	BMD (BMDL) by Excess Risk Level	
			1/10 [b]	1/1000 [c]
Tumors excluding cystic keratinizing squamous lesions				
Male	8	0.73	1.07 (0.81)	0.011
Female			1.04 (0.93)	0.010
All tumors				
Male	8	0.35	1.01 (0.78)	0.010
Female			0.85 (0.75)	0.0085

[a] Data are from two studies of fine TiO_2 [Lee et al. 1985; Muhle et al. 1991] and one study of ultrafine TiO_2 [Heinrich et al. 1995].
[b] Estimated directly from model.
[c] Estimated from linear extrapolation of BMD and BMDL at 1/10 excess risk level.

APPENDIX E

CALCULATION OF UPPER BOUND ON EXCESS RISK OF LUNG CANCER IN AN EPIDEMIOLOGIC STUDY OF WORKERS EXPOSED TO TiO_2

Results from two epidemiologic studies [Fryzek et al. 2003, 2004a,b; Boffetta et al. 2003, 2004] were used to compute the upper bound estimates of excess lung cancer risk. The excess risks for lung cancer corresponding to the upper limit of a two-sided 95% CI on the RR associated with cumulative exposure to total TiO_2 dust in U.S. workers were based on results supplied by Fryzek [2004] for Cox regressions fitted to cumulative exposures viewed as a time-dependent variable. The provided results include the coefficients and standard errors for the continuous model for cumulative exposure [Fryzek 2004]. For a study of United Kingdom and European Union workers exposed to respirable TiO_2 [Boffetta et al. 2004], excess risks for lung cancer were not available, and therefore were derived from the results provided in a detailed earlier report Boffetta et al. [2003], as follows. The excess risk estimates computed from each of these epidemiologic studies were then used in Appendix F for comparison to the rat-based excess risk estimates for humans (Chapter 4).

Methods

Categorical results on exposure-response are reported in Tables 4.1 (SMRs) and Table 4.2 (Cox regressions) of Boffetta et al. [2003]. There are four categories, i.e., 0-0.73, 0.74-3.44, 3.45-13.19, 13.20+ (mg/m^3•yr) in these results, and the maximum observed exposure is 143 mg/m^3•yr (Table 2.8 of Boffetta et al. [2003]). Hence, the midpoints of the categories are 0.365, 2.09, 8.32, 78.1 mg/m^3•yr. The value of the highest category depends on the maximum observed value

and is subject to considerable variability. An alternate value for this category is 56.5 mg/m^3•yr. This value is based on estimating the conditional mean cumulative exposure given that the exposure exceeds 13.20 using the lognormal distribution that has median 1.98 and 75th percentile equal to 6.88 based on results in Table 2.8 (*Overall*). Results are generated using both 78.1 and 56.5 mg/m^3•yr to represent the highest exposure group. The SMRs reported in Table 4.1 were modeled as follows:

E[SMR] = Alpha*(1+Beta*CumX) where SMR = Y/E is the ratio of the observed to the expected count.

=> E[Y] = Alpha*(1+Beta*CumX)*E fitted to observed counts (Y) by iteratively reweighted least squares (IRLS) with weights proportional to 1/E[Y].

Notes:

Beta describes the effect of cumulative exposure, CumX, and Alpha allows the cohort to differ from the referent population under unexposed conditions.

The estimators of Alpha and Beta are based on iteratively re-weighted least squares with weights proportional to the reciprocal of the mean. Although these estimates are equivalent to Poisson regression MLEs, the observed counts are not strictly Poisson. This is due to the adjustments made by Boffetta et al. [2003] for missing cause of death arising from the limited time that German death certificates were maintained. The reported *observed* counts are 53+.9, 53+2.3, 52+2.7, 53+2.4 where 0.9, 2.3, 2.7 and 2.4 have been added by Boffetta et al. [2003] for missing cause of death that are estimated to have been lung cancer deaths. Invoking a Poisson regression model should work well given such small adjustments having been added to Poisson counts of 53, 53, 52 and 53. Hence, Alpha and Beta are estimated accordingly but their standard errors and CIs do not rely on the Poisson assumption; instead,

standard errors were estimated from the data and CIs were based on the t distribution with 2 degrees of freedom.

A similar approach using the results of Table 4.2 was not attempted since these categorical RR estimates are correlated and information on the correlations was not reported by Boffetta et al. [2003].

Results

Results based on modeling the SMRs in Table 4.1 of Boffetta et al. [2003] with a linear effect of cumulative exposure are presented in Table E-1. These results are sensitive to the value used to represent the highest cumulative exposure category, particularly the estimate of the effect of exposure. However, zero is contained in both of the 95% CIs for Beta indicating that the slope of the exposure-response is not significant for these data.

Estimates of excess risk based on application of the results given in Table E-1 to U.S. population rates using the method given by BEIR IV [1988] appear in Table E-2.

Discussion

The exposure assessment conducted by Boffetta et al. [2003] relies heavily on tours of the factories by two occupational hygienists who first reconstructed historical exposures without using any measurements (as described in Boffetta et al. [2003]; Cherrie et al. [1996]; Cherrie [1999]; Cherrie and Schneider [1999]). The sole use of exposure measurements by Boffetta et al. [2003] was to calculate a single adjustment factor to apply to the previously constructed exposure estimates so that the average of the measurements coincided with the corresponding

reconstructed estimates. However, Boffetta et al. [2003] offer no analyses of their data to support this approach. Also, the best value to use to represent the highest exposure interval (i.e., *13.20+* $mg/m^3 \cdot yr$) is not known and the results for the two values examined suggest that there is some sensitivity to this value. Hence, these upper limits that reflect only statistical variability are likely to be increased if the effects of other sources of uncertainty could be quantified.

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Table E-1. Results on Beta from modeling the SMRs reported in Table 4.1 of Boffetta et al. [2003] for the model, E[SMR] = Alpha*(1+Beta*CumX)

Value Representing Highest CumX	Beta[a] Estimate	Approx Std Error	Approximate 95% Confidence Limits	
78.1	0.000044	0.00163	-0.00697	0.00706
56.5	0.000109	0.00229	-0.00975	0.00996

(a) Beta is the coefficient for the effect of 1 mg/m^3•yr cumulative exposure to respirable TiO_2 dust.

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Table E-2. Lifetime excess risk after 45 years of exposure estimated by applying the above UCLs on Beta and the linear relative rate model of lung cancer to U.S. population rates (a).

Occupational exposure (8-hr TWA respirable mg/m^3)	Background risk (Ro)	Beta=0.000044 Excess risk (b) (Rx-Ro)	UCL=0.00706 Excess risk (b) (Rx-Ro)	Beta=0.000109 Excess risk (c) Rx-Ro)	UCL=0.00996 Excess risk (c) (Rx-Ro)
0.0	0.056	0	0	0	0
1.5		0.0002	0.024	0.0004	0.033
5.0		0.0005	0.076	0.0012	0.11
15.0		0.0015	0.21	0.0037	0.27

a. Based on the method given by BEIR IV using U.S. population rates given in Vital Statistics of the U.S. 1992 Vol II Part A [NCHS 1996]. Occupational exposure from age 20 through age 64 and excess risks subject to early removal by competing risks are accumulated up to age 85.

b. Value representing the highest exposure category is 78.1 mg/m^3 yr based on the midpoint of the interval [13.20, 143].

c. Value representing the highest exposure category is 56.5 mg/m^3 yr based on the conditional mean given exposures greater than 13.20 using the conditional distribution derived from the lognormal distribution having median and 75th percentiles equal to 1.98 and 6.88 mg/m^3 yr, respectively.

APPENDIX F

COMPARISON OF RAT- AND HUMAN-BASED EXCESS RISK ESTIMATES FOR LUNG CANCER FOLLOWING CHRONIC INHALATION OF TiO_2

As described in Chapter 2, the epidemiologic studies of workers exposed to TiO_2 did not find a statistically significant relationship between the estimated exposure to total or respirable TiO_2 and lung cancer mortality [Fryzek et al. 2003; Boffetta et al. 2004]. However, the power of these studies is also insufficient to detect excess risks of concern for worker health (e.g., $\leq$1/1000). In addition, the exposure data in these studies was primarily based on the total dust fraction; limited data were available for exposure to respirable particles, and no data were available on exposures to ultrafine particles. Chronic inhalation studies in rats exposed to fine [Lee et al. 1985] and ultrafine TiO_2 [Heinrich et al. 1995] showed statistically significant dose-response relationships for lung tumors (Chapter 3). However, the rat lung tumor response at high particle doses that overload the lung clearance has been questioned as to its relevance to humans [Watson and Valberg 1996; Warheit et al. 1997; Hext et al. 2005]. Recent studies have shown that rats inhaling TiO_2 are more sensitive than mice and hamsters to pulmonary effects including inflammation [Bermudez et al. 2002, 2004], although the hamsters had much faster clearance and lower retained lung burdens of TiO_2 compared to rats and mice. Because of the observed dose-response data for TiO_2 and lung cancer in rats, it is important to quantitatively compare the rat-based excess risk estimates with excess risk estimates derived from results of the epidemiologic studies.

The purpose of these analyses is to quantitatively compare the rat- and human-based excess risks of lung cancer by using hypothesis tests with results from the human and rat studies. If the sensitivity of the rat response to inhaled particulates differs from that of humans, then the excess risks derived from the rat data would be expected to differ from the excess risks estimated from the human studies. The results of the tests will be used to assess whether or not the observed differences of excess risks have adequate precision for reasonably excluding the rat model as a basis for predicting the excess risk of lung cancer in humans exposed to TiO_2.

Methods

Excess risk estimates for lung cancer in workers were derived from the epidemiologic studies (Appendix E) and from the chronic inhalation studies in rats [Heinrich et al. 1995; Lee et al. 1985]. These excess risk estimates and associated standard errors were computed for a mean exposure concentration of 0.044 or 1.5 mg/m^3 over a 45-year working lifetime. These exposure concentrations were selected to correspond, respectively, to the average exposure reported in Boffetta et al. [2004] and to a low value relative to the rat data (which is also the NIOSH REL, Chapter 4). Excess risks were derived from the rat data based on a logistic regression model for each gender using two different methods. One method used a logistic model to characterize the dose-response relationship over the full range of doses. The other method used the logistic model to estimate a benchmark dose (BMD) corresponding to a 10% excess risk, followed by linear extrapolation to lower doses.

Excess risks were estimated from each of the two worker cohort studies, using two different methods for each. For the cohort studied by Boffetta et al. [2004], two different values for

representing the highest cumulative exposure group were separately assumed; and for the cohort studied by Fryzek et al. [2003], two different exposure lags (no lag, 15 year lag) were separately used. Each comparison is based on a statistical hypothesis test of equality of the expectations of these estimates with the test statistic being their difference divided by the standard error. For the Fryzek cohort the test statistic is referred to a standard normal distribution based on large sample theory. For the Boffetta study the standard error of the difference is based on treating the variance of the Boffetta-derived excess risk as unknown and estimated (Appendix E), and the rat-based variance is treated as approximately known based on large sample theory; the variance of the difference is hence estimated and the corresponding degrees of freedom of the estimate is based on Satterthwaite's formula [Gaylor 1988] in referring the test statistic to a student's t distribution. Each test compared an excess risk derived from a rat study to an excess risk derived from one of the cohort studies. The pairwise tests are for two-tailed alternatives and are not adjusted for multiple comparisons; such an adjustment would have reduced the power for rejecting the rat model as a basis for extrapolating to humans.

Results

Tables F-1 and F-2 show the rat-based maximum likelihood estimates (MLE) of excess risks for lung cancer and the human-based 95% UCL on excess risk from exposure to TiO_2. There is consistency in the estimates of the 95% UCL from these two independent epidemiologic studies at the exposure concentration evaluated for both studies, 1.5 mg/m^3 (Boffetta: 0.024 and 0.033; Fryzek: 0.029 and 0.035). Table F-1 provides rat-based estimates using a logistic regression model (Appendix A) to directly estimate the excess risk (which allows curvature in the low-dose region), and Table F-2 provides rat-based estimates using linear extrapolation from the

benchmark dose estimates at 10% excess risk (Tables 4-5 and D-1). Both Tables F-1 and F-2 include estimates using rat response data on the lung for either "all tumors" or "tumors excluding squamous cell keratinizing cysts."

Tables F-1 and F-2 compare the rat-based MLE excess risk estimates for lung cancer to the 95% UCL estimates from the epidemiologic studies. The rat-based estimates for lung mass or lung surface area extrapolation and fine or ultrafine TiO_2 exposures are all lower than the 95% UCL risk estimates based on the human studies in Table F-1. For the rat-based excess risk estimates using linear extrapolation from the benchmark dose estimates (Table F-2), most MLEs are below the 95% UCL estimates from the human studies; however, the rat-based MLE excess risk estimates for ultrafine TiO_2, using the lung surface area extrapolation, are slightly above one or more of the 95% UCL estimates from the human studies. The comparisons based on omitting the squamous keratinizing cysts were also significant when compared to the excess risk derived using 78.1 mg-yr/m^3 to represent the highest exposure group of the cohort studied by Boffetta; when substituting 56.5 mg-yr/m^3 the comparisons were not quite significant (P =.06). When comparing ultrafine TiO_2 using the lung surface area extrapolation to results derived from the cohort studied by Fryzek, only the model based on a 15-year lag was suggestive ($0.050 < P < 0.090$) of higher excess risks derived from rat data under these assumptions.

Discussion

These two epidemiologic studies are subject to considerably larger variability than are the rat studies. The results of the epidemiologic studies of TiO_2 workers by Fryzek et al. [2003] and Boffetta et al. [2003, 2004] are consistent with a range of excess risks at given exposures,

including the null exposure-response relationship (i.e., no association between the risk of lung cancer and TiO_2 exposure) and an exposure-response relationship consistent with the low-dose extrapolations from the rat studies (based on the methods used, either a logistic model or linear extrapolation from the 10% BMD). The MLE excess risk estimates from the rat studies were lower than the 95% UCL from the human studies for both fine and ultrafine TiO_2 when the rat estimates were based on the logistic model and either extrapolation approach (Table F-1). When the linear extrapolation from the 10% BMD was used, the rat MLE estimates were also generally lower than the 95% UCL from the human studies--except for the rat MLE estimates for ultrafine TiO_2 based on the lung surface area extrapolation, which were the same or slightly higher than some of the human study estimates (Table F-2).

Comparison of the excess risk estimates from the human and rat studies was accomplished by testing whether their difference departed significantly from zero; this test used the standard error of the difference, which reflects variability in both the human data and the rat data. The results of these tests show that the nonsignificant exposure-responses of the human studies are also consistent with the excess risks extrapolated from rats exposed to fine TiO_2 particles, but the tests involving rats exposed to ultrafine TiO_2 show that extrapolations based on surface area may overpredict the excess risks in these two cohorts of workers. However, information about the size distribution of the workers' exposures is not available.

The Fryzek et al. [2003] study used total dust exposure estimates. If the airborne dust had included some fraction of particles larger than respirable size, then the human exposures to the respirable TiO_2 would be overestimated. If a multiplicative factor to adjust the total dust exposures to the respirable exposures were available then the effect would be to increase the

current upper confidence limit estimate. However, the rat-based estimates are generally already within the confidence interval estimates of the human excess risk estimates. Therefore, the interpretation that the results from Fryzek et al. [2003] are consistent with the potency extrapolated from the rats would not change.

The median working lifetime exposure in Boffetta et al. [2003] was relatively low—median estimated cumulative exposure was 1.98 mg-yr/m^3, which is equivalent to 0.044 mg/m^3 over a 45-year working lifetime. The upper confidence limit on excess risk at that concentration was also estimated to be quite low, approximately an order of magnitude lower than the excess risk predicted to be observable in a typical epidemiologic study [Stayner and Smith 1993]. This suggests that the exposures and risk estimates in the Boffetta et al. study [2004] are sufficiently low such that a significant dose-response relationship for TiO_2 exposure and lung cancer would not be expected to be observed. The Fryzek et al. [2003] study did not include sufficient information to estimate the median exposure for the cohort, and neither the Boffetta et al. [2004] nor the Fryzek et al. [2003] study provided information on the study power.

In conclusion, the comparison of the rat- and human-based excess risk estimates for lung cancer indicates that the rat-based estimates for exposure to fine TiO_2 particles are not inconsistent with those from the human studies. Therefore, it is not possible to exclude the rat model as an acceptable model for predicting lung cancer risks from TiO_2 exposure in workers without further knowledge of the particle sizes of their exposures.

Table F-1. Comparison of rat-based excess risk estimates (MLE) for lung cancer from TiO_2 (using a logistic regression model) with the 95% upper confidence limit (95% UCL) of excess risk of lung cancer in workers, at low exposure concentrations, for a 45-year working lifetime.[a]

TiO_2 mean concentration (mg/m^3) over 45-year working lifetime	Human-based excess risk (95% UCL): *two different estimates* from Boffetta et al. [2003, 2004]	Human-based excess risk (95% UCL): *two different estimates* from Fryzek et al. [2003]	Rat-based excess risk (MLE): Fine TiO_2 (*1st value: male. 2nd value: female*)		Rat-based excess risk (MLE): Ultrafine TiO_2 (*1st value: male. 2nd value: female*)	
			Lung mass extrapolation	Lung surface area extrapolation	Lung mass extrapolation	Lung surface area extrapolation
			All tumors			
0.044	0.00071[b] 0.0010[c]	(not determined)	0.000013 0.0000062	0.000036 0.000017	0.00011 0.000054	0.00032 0.00015
1.5	0.024[b] 0.033[c]	0.035[d] 0.029[e]	0.00043 0.00020	0.0013 0.00061	0.0043 0.0022	0.014 0.0085
			Tumors without squamous cell keratinizing cysts			
0.044	0.00071[b] 0.0010[c]	(not determined)	0.000013 0.0000046	0.000034 0.000012	0.00011 0.000040	0.00031 0.00011
1.5	0.024[b] 0.033[c]	0.035[d] 0.029[e]	0.00041 0.00015	0.0012 0.00045	0.0041 0.0016	0.013 0.0058

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Footnotes for Table F-1:

* Indicates value exceeds one or more excess risk estimate from the human data (none in this table).

[a] *Methods notes:* The value of 0.044 mg/m^3 is the median concentration (over 45-years) from Boffetta et al. [2003, 2004]. The median concentration was not determinable from the information in Fryzek et al. [2003]. The value of 1.5 mg/m^3 is a low value relative to the rat study. The MPPD human lung dosimetry model [CIIT RIVM 2002] was first used to estimate the lung burden after 45-years of exposure to a given mean concentration. The estimated retained particle mass lung burden was extrapolated from human to an equivalent particle surface area lung burden in rats, based on species differences in either the mass or surface area of lungs, and using specific surface area values of TiO_2 for fine (6.68 m^2/g) or ultrafine (48 m^2/g). The rat dose-response model (modified logistic, Appendix A) was then used to estimate the excess risk of lung cancer at a given dose.

[b] From Boffetta et al. [2003, 2004)] assumed 78.1 mg-yr/m^3 in highest cumulative exposure group (respirable TiO_2).

[c] From Boffetta et al. [2003, 2004], assumed 56.5 mg-yr/m^3 in highest cumulative exposure group (respirable TiO_2).

[d] From Fryzek et al. [2003, 2004a,b]; Fryzek [2004] unlagged model (total TiO_2).

[e] From Fryzek et al. [2003, 2004a,b]; Fryzek [2004] model with 15-year lag (total TiO_2).

Table F-2. Comparison of rat-based excess risk estimates (MLE) for lung cancer from TiO_2 (using linear extrapolation of benchmark dose at 10% excess risk) with the 95% upper confidence limit (95% UCL) of excess risk of lung cancer in workers, at low exposure concentrations, for a 45-year working lifetime.[a]

TiO_2 mean concentration (mg/m^3) over 45-year working lifetime	Human-based excess risk (95% UCL): *two different estimates* from Boffetta et al. [2003, 2004]	Human-based excess risk (95% UCL): *two different estimates* from Fryzek et al. [2003]	Rat-based excess risk (MLE): Fine TiO_2 (*1st value: male. 2nd value: female*)		Rat-based excess risk (MLE): Ultrafine TiO_2 (*1st value: male. 2nd value: female*)	
			Lung mass extrapolation	Lung surface area extrapolation	Lung mass extrapolation	Lung surface area extrapolation
			All tumors			
0.044	0.00071[b] 0.0010[c]	(not determined)	0.000032 0.000042	0.000088 0.00011	0.00028 0.00036	0.00078* 0.0010
1.5	0.024[b] 0.033[c]	0.035[d] 0.029[e]	0.0010 0.0014	0.0030 0.0039	0.0098 0.013	0.027* 0.035*
			Tumors without squamous cell keratinizing cysts			
0.044	0.00071[b] 0.0010[c]	(not determined)	0.000029 0.000030	0.000070 0.000081	0.00026 0.00026	0.00072* 0.00072*
1.5	0.024[b] 0.033[c]	0.035[d] 0.029[e]	0.0010 0.0010	0.0027 0.0028	0.0088 0.0090	0.024 0.024

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Footnotes for Table F-2:

* Indicates value exceeds one or more excess risk estimate from the human data.

[a] *Methods notes:* The value of 0.044 mg/m^3 is the median concentration (over 45-years) from Boffetta et al. [2003, 2004]. The median concentration was not determinable from the information in Fryzek et al. [2003]. The value of 1.5 mg/m^3 is a low value relative to the rat data. The MPPD human lung dosimetry model [CIIT RIVM 2002] was first used to estimate the lung burden after 45-years of exposure to a given mean concentration. The estimated retained particle mass lung burden was extrapolated from human to an equivalent particle surface area lung burden in rats, based on species differences in either the mass or surface area of lungs, and using specific surface area values of TiO_2 for fine (6.68 m^2/g) or ultrafine (48 m^2/g). The rat dose-response model (using linear extrapolation of benchmark dose at 10% excess risk) was then used to estimate the excess risk of lung cancer at a given dose. Bayesian model average of the multiple benchmark dose estimates was used (see Tables 4-5 and D-1).

[b] From Boffetta et al. [2003, 2004], assumed 78.1 mg-yr/m^3 in highest cumulative exposure group (respirable TiO_2).

[c] From Boffetta et al. [2003, 2004], assumed 56.5 mg-yr/m^3 in highest cumulative exposure group (respirable TiO_2).

[d] From Fryzek et al. [2003, 2004a,b]; Fryzek [2004] unlagged model (total TiO_2).

[e] From Fryzek et al. [2003; 2004a,b]; Fryzek [2004] model with 15-year lag (total TiO_2).