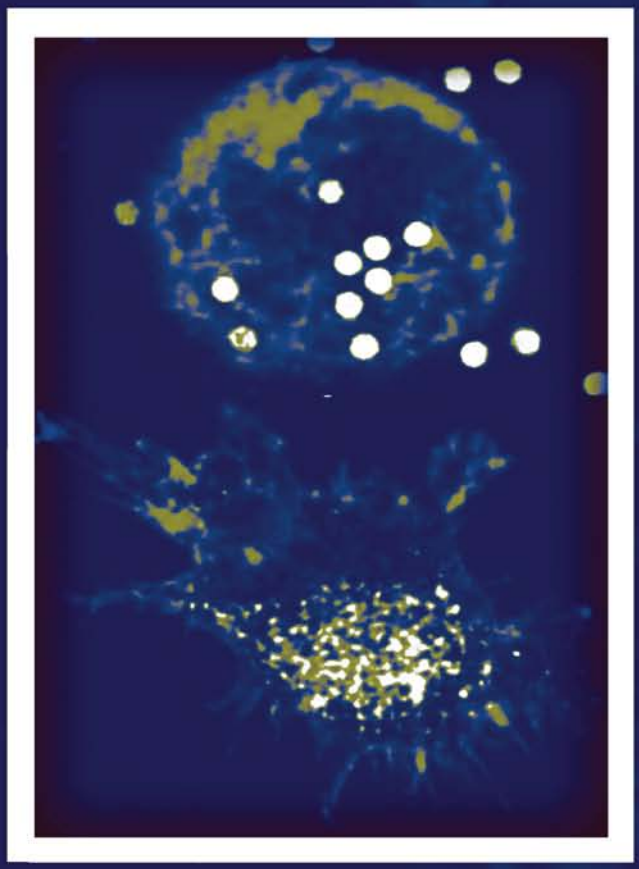
Particle Toxicology



Edited by
Ken Donaldson
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CRC Press
Taylor & Francis Group

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an informa business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20130725

International Standard Book Number-13: 978-1-4200-0314-7 (eBook - PDF)

Foreword

The association between lung diseases and the inhalation of dusts has been recognized throughout history, stretching back to Agricola and Paracelsus in the fifteenth and sixteenth centuries. Needless to say the scientific endeavour associated with identifying the relationship between particle characteristics and pathological processes—the essence of modern particle toxicology—awaited the development of a contemporary understanding of both lung disease and the physicochemical nature and aerodynamic behaviour of particles. These elements finally came together in the mid-twentieth century and modern approaches to understanding harmful inhaled particles can be first traced to quartz (crystalline silica) and its fibrogenic effects in the lungs. Undeniably, in a truly applied toxicology approach to the notion that the surface reactivity of quartz was the harmful entity, a whole programme of toxicology-based therapy was undertaken, using aluminium to attempt to reduce the harmfulness of the quartz in already exposed subjects.

Meanwhile the epidemic of disease caused by asbestos, the other particle source of the twentieth century, was taking hold and by late- to mid-twentieth century, an understanding of the toxicology of asbestos began. The full understanding of the asbestos hazard was, however, only realised in the 1980s and 1990s, following the rise in use of synthetic vitreous fibres in the years following the reduction in asbestos use. In these years, ground-breaking studies demonstrated the importance of length and biopersistence, which explained differences between asbestos types and placed all respirable mineral fibres in a single toxicology paradigm that embraced both asbestos and the synthetic vitreous fibres.

In the 1990s, ambient particulate matter as a regulated air pollutant (PM_{10}[1]) became the focus of global concern. This was initiated by epidemiological studies that were now able to process huge data sets on air quality and human morbidity and mortality. Both cohort and time-series studies in many countries associated substantial premature mortality and excess morbidity in urban residents to their air pollution exposure, with particles as the most potent component of the air pollution cocktail. Although the risks are low, particulate matter affects the whole population and the effects were still preset below the air quality standards. It also became evident that certain groups, such as elderly and people with respiratory and cardiovascular diseases, were at increased risk. Since then, particle toxicologists are faced with the fact that PM_{10} is a complex mixture by itself, whereas the risks identified in the epidemiologic studies are based on total mass concentrations. A further reduction of the PM levels would be very expensive and a cost effective strategy was warranted. There was an urgent need to identify the causal relationship between PM, (personal) exposure and associated health effects. This recognition stimulated governments globally, and new funding flowed into particle toxicology research to identify the critical aspects that could be linked with the health effects observed in epidemiological studies. It soon became clear that no single, omnipresent constituent could be identified that related to the variety of health effects. It turned out to be a big challenge for many because of the variability in PM_{10} (size range, surface chemistry, agglomeration, shape, charge, chemical composition, et cetera), the focus on susceptibility factors (disease, age, and gender) and the lack of good *in vitro* and animal models to mimic these factors.

The increasing emphasis of PM toxicology on the cardiovascular system as a key target for adverse effects brought an entirely new dimension. Particle toxicologists were forced to move out of their comfort zone in the respiratory tract and try to understand how inhaled particles could also affect the cardiovascular system or other target tissues such as the brain. At the end of the twentieth century and the dawn of the twenty-first century, manufactured nanoparticles[2] have come to

[1] Defined as mass of particles centered around an aerodynamic diameter of 10 μm.

[2] Generally defined as particles with at least one dimension less than 100 nm.

represent the new frontier for particle toxicologists based on nanotechnology's potential to produce a wide range of new particles varying in size and chemistry. Traditionally, particle dosimetry has always been linked with particle toxicology, due to the complex relationship between exposure and target dose. Unexpected translocation of nanoparticles from the respiratory system to other organs and a recognition that manufactured nanoparticles could affect the skin and the gut—depending on the type of exposure—have extended the area of research.

Throughout the fifty or so years that have seen the full flowering of the scientific discipline of particle toxicology, particle toxicologists have looked to mainstream molecular biology for their pathobiological paradigms, with the examples intra-cellular signalling pathways, inflammation biology, immunomodulation, and genotoxicity as prime examples. They have also looked to chemistry and physics for an improved understanding of the particle characteristics that drive toxicity, including the assessment of free radical production and oxidative stress—a leading paradigm for how particles affect cells. In addition they have worked in tandem with aerosol physicists and modellers to develop the dosimetric models that are so important, including the role of aerodynamic diameter in dictating the site of the deposition of particles. Particle toxicologists have also worked with epidemiologists and most recently with cardiologists and neurologists, and the net result has been to produce a truly multidisciplinary science that uses computational modelling, *in vitro* techniques, and animal and human studies to address their hypotheses.

This volume represents the view of a number of world's leading particle toxicologists in their chosen specialties, many of whom were involved in the events described above and in raising particle toxicology to the status that it has today. Their chapters address the most important aspects of particle toxicology and confirm its status as a mature science. As such, I believe that this volume is a database that provides not only a historical view, but most of all state-of-the-science concepts in a single volume. It covers the broad spectrum of particle toxicology from particle characterization, respiratory tract dosimetry, cellular responses, inflammation, fibrogenesis, cardiovascular and neurological effects, and genotoxicity. The chapters cover all kind of particle types, unlike previous books that have focused on single particle types, such as quartz or fibres and so forms an essential reference work. Particle toxicology is different from any other toxicology. Different in the sense that it has demonstrated that "dose," as defined by Paracelsus, has more dimensions than mass per volume. The book deals with the specific nature of particle toxicology in great detail, and I truthfully believe that this volume will provide the reader with a unique and practical insight into this fascinating branch of toxicology.

On behalf of the editors, Ken Donaldson and Paul Borm, I would like to thank the authors for their generous time in writing the chapters and the staff of Taylor & Francis for their excellent support in the production of the book.

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Preface

The toxicology of particles is an absorbing area of research in which to work and when we conceived this book, we wanted to capture some of the fascination that we feel about our profession.

We are well-pleased with the result—everyone we invited to write a chapter agreed and almost everyone delivered a manuscript—a remarkable outcome in this time of conflicting deadlines. It is difficult to keep up with the sheer quantity of data that accumulates on particle toxicology. This has resulted in polarisation of meetings and specialists into particle types, thus there are meetings on PM or nanoparticles and there can be inadequate cross-talk. This is unfortunate because of the benefits of understanding the toxicology of one particle type for understanding other particle types. This volume deals with all particle types and offers state-of-the-science reviews that should benefit practitioners of the many disciplines who are involved in particle toxicology. Particle toxicology is a "work in progress," as witnessed by the rise of nanoparticle toxicology, and has become an important area of endeavour in toxicology, pollution science, respiratory medicine and increasingly, cardiovascular medicine. This book is, therefore, timely and apposite to meeting this need for information.

We warmly thank the authors who have been involved in writing the various chapters of this book and the staff of Taylor & Francis for their invaluable and professional assistance in its realisation.

Ken Donaldson
Paul Borm

Editors

Professor Dr. Paul J.A. Borm has been with the Centre of Expertise in Life Sciences (CEL) at Zuyd University in Heerlen, The Netherlands since 2003. Although his research work has concentrated mostly on lung diseases, his activities and coordination have always included a larger array of subjects related to (occupational) health care. He is the author of more than 160 peer reviewed papers and more than 150 oral presentations on topics in occupational and environmental toxicology. Professor Borm is a member of the German MAK-commission and the Dutch Evaluation committee on Occupational Substances (DECOS). He has been an invited member of expert groups such as IARC (1996), ILSI (1998), and ECVAM (1997), and he has been the organizer of many international meetings and workshops on occupational risk factors. He is an editorial board member for *Human Experimental Toxicology* and *Inhalation Toxicology* and a co-editor of *Particle and Fibre Toxicology*.

The combination of his know-how in pharmacology, toxicology, and management of interdisciplinary research projects and teams are among his skills. In his current function at Zuyd University, he is trying to interface fundamental and applied sciences with developments and needs in the public and private sector, such as health care, functional foods, and nanotechnologies. Dr. Borm is involved in a number of large-scale projects including education in nanotechnology, technology accelerator using nanotechnology, and cell therapy. Apart from his position at Zuyd, Borm holds management contracts with start-ups (Magnamedics GmbH) and grown-ups in Life Sciences. Drug delivery and/or toxicological testing of drug delivery tools are core businesses in these activities.

Ken Donaldson is professor of respiratory toxicology in the Medical School at the University of Edinburgh, where he is co-director of the Edinburgh Lung and the Environment Group Initiative Colt Laboratory—a collaborative research institute involving the Edinburgh University Medical School, Napier University, and the Institute of Occupational Medicine, carrying out research into disease caused by inhaled agents, predominantly particles.

He has carried out 27 years of research into the inhalation toxicology of all medically important particle types—asbestos, man-made vitreous fibres, crystalline silica, nuisance dusts, ultrafine/nanoparticles, particulate air pollution (PM10), and organic dust, as well as ozone and nitrogen dioxide. He is a co-author of over 250 peer-reviewed scientific articles, book chapters, and reviews on lung disease caused by particles and fibres. Dr. Donaldson is a member of three government committees—COMEAP (Committee on the Medical Effects of Air Pollution), which advises the government on the science of air pollution; EPAQS (Expert Panel on Air Quality Standards), which provides independent advice to the government on air quality issues (ad hoc member); and the Advisory Committee on Hazardous Substances, which provides expert advice to the government on the science behind hazardous chemicals. He has advised WHO, EU, US EPA, UK, HSE, and other international bodies on the toxicology of particles. He is a registrant of the BTS/IOB Register of Toxicologists, a Eurotox-registered toxicologist, a Fellow of the Royal College of Pathologists, a Fellow of the Society of Occupational Medicine, and he has a DSc for research in toxicology of particle-related lung disease. He is the founding editor in chief, along with Paul Borm, of the journal *Particle and Fibre Toxicology*.

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Table of Contents

1 An Introduction to Particle Toxicology: From Coal Mining to Nanotechnology

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CONTENTS

1.1 HISTORICAL DEVELOPMENT OF PARTICLE TOXICOLOGY

Particle research and particle toxicology have been historically closely connected to industrial activities or materials, such as coal, asbestos, manmade mineral fibers, and more recently, ambient particulate matter (Donaldson and Borm 2000) and Nanotechnology (Donaldson 2004; Kurath 2006). The Middle ages saw the first recordings of ill health associated with mining in the writings of Agricola (1494–1555) and Paracelsus (1493–1541), who noted lung diseases in miners in Bohemia and Austria, respectively (Seaton 1995). Initial studies in the modern era concerned workers employed in the coal mining and coking industry, a widespread industry producing, transporting, or burning large amounts of coal. During these processes large quantities of particles were generated, and historically, exposures to coal and coal mine dust have been described as attaining 40 mg/m^3, whereas in current mining a standard of 2–3 mg/m^3 is well maintained (Figure 1.1).

Nowadays, research on particles largely concentrates on exposure to ambient particulate matter (PM) at concentrations between 10 and 50 μg/m^3. Among these particles, the fine and the ultrafine fraction ($<$100 nm) are considered to be the most harmful (Peters et al. 1997a; Donaldson et al. 2005), although consensus is not yet reached as to the relative role of the different size fractions. The term ultrafine particles has gradually become intertwined with the term nanoparticles, since they embrace the same size range as particles produced by current nanotechnology (Buxton et al. 2003; Ferrari 2005).

This book contains reviews on the mechanisms and properties of various materials that we are exposed to in particulate form. Both the order and the content will allow the reader to achieve a

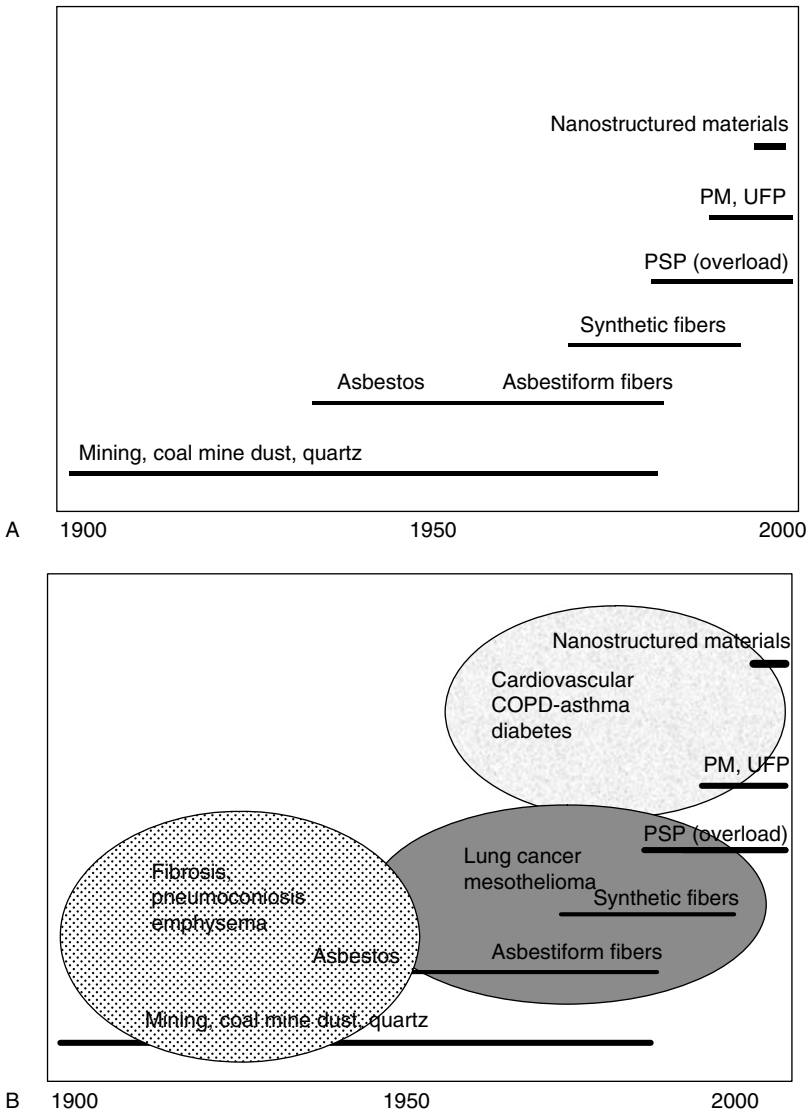

FIGURE 1.1 Historical development of particle toxicology along with technologies and (major) toxicological products emerging from these technologies. Panel A: time frame of particles driving particle toxicology, Panel B: particles along with the major outcomes that were studied.

comprehensive understanding of how particles may cause adverse health effects. These actions may be related to the material, the particulate or fibrous shape, or the specific site of deposition or translocation. This introductory chapter will try to give a brief overview of developments of particle research, from a historical perspective, from coal mining, fiber-related diseases, and ambient particulate matter to hazards imposed by nanomaterials.

1.2 THE IMPACT OF COAL AND ASBESTOS ON RESEARCH AND REGULATION

Coal mining is one of the oldest occupational activities that was, and still is, performed on a large scale. Apart from offering tremendous economic and political benefits, coal mining carried dangers from exposure to noise, heat, and airborne dusts, causing many associated diseases. Respiratory

diseases caused by coal mine dust are well known from epidemiological studies in the past century and include coal workers' pneumoconiosis (review: Heppleston 1992), but also chronic bronchitis (review: Wouters et al. 1994) and emphysema (Ruckley et al. 1984; Leigh et al. 1994). The classical industrial use of coal was its heating and conversion into coke, a hard substance consisting of purely carbon. Coke ovens can be seen all over the Ruhr area and were the starting point of fertilizer production. If coke is combined with iron ore and limestone, the mixture is then heated to produce iron, which explains the combined appearance of coal mines, coke ovens, and the steel industry. Therefore, it should also be no surprise that the European Community for Steel and Coal (ECSC) was founded in 1951. Up to 1999, the ECSC was the steering agency for research on particle (i.e., coal) induced respiratory diseases in Europe. During its existence, the ECSC ran five different medical research programs with a total budget of 35.3 million euro. In its slipstream, well-known research institutes were built, of which few survive today. Their research has played a major role in producing extensive epidemiological data, the exploration of mechanisms in particle deposition (e.g., Chapter 3) and particle-induced lung diseases (e.g., Chapter 12 and Chapter 23), and by a combination of the two, performed work to explain the large inter-individual differences in disease rates between miners and coalmines. A lot of this work was based on the hypothesis that the crystalline silica (quartz) content in respirable coal mine dust was the principal agent in coal particles mediating their adverse effects. This approach also deserves some historical explanation.

The epidemic of lung disease caused by asbestos has substantially occupied particle toxicologists and continues to resonate in modern society. In the West, where asbestos is effectively regulated out of use or banned, there is a continuing rise in deaths from mesothelioma. This has been well documented all over Europe with a peak showing a 30–40 year lag pro rata with the peak of amphibole exposures (Peto et al. 1995; McElvenny et al. 2005, U.K. data). However, in the less developed world, asbestos exposure and disease burden is also increasing (Kazan-Allen 2005). Toxicologists have made a huge contribution to understanding the nature of the fiber hazard. Wagner, using erionite, showed importantly that asbestos fibers were not the only fiber capable of causing mesothelioma (Wagner et al. 1985). However, it was the rise in the use of the synthetic vitreous fibers (SVF) as replacements for asbestos that really allowed a full understanding of fiber toxicology and the unification of fiber toxicology into one understanding that embraces both asbestos and the SVF. The RCC studies on SVF were a groundbreaking set of studies that compared a number of SVF of different composition at similar length, for their pathogenicity long-term rat studies (Mast et al. 1995; Hesterberg et al. 1996; Hesterberg et al. 1998; McConnell et al. 1999). In brief, these state-of-the-science studies identified the key role of biopersistence and length in mediating adverse effects of particles and fibers. This shed light on the observation that chrysotile had been reported to be generally less harmful than the amphiboles and that in the lungs of chrysotile miners, the dominant recoverable fiber was in fact amphibole (McDonald et al. 1997). This reflected the greater solubility of chrysotile in the lung milieu—a direct consequence of its Swiss-roll structure and its acid-soluble brucite layer (Bernstein et al. 2003; Wypych et al. 2005). The importance of biopersistence in modulating the pathogenicity of long thin fibers was sealed with its enshrinement in European Legislation, which allow nonbiopersistent SVF to be exonerated as carcinogens, based on having composition that renders them soluble or following adequate testing (Council of the European Union 1997). During this time, Mossman and coworkers made considerable advances in demonstrating that asbestos could activate key oncogenes in epithelial cells, hinting at direct carcinogenic effects driven by oxidative stress (Heintz et al. 1993; Janssen et al. 1995) whilst the proinflammatory effects and their size-related effects were clearly demonstrated (Donaldson et al. 1988; Donaldson et al. 1989; Petruska et al. 1991; Ye et al. 1999) providing support for indirect carcinogenesis acting through inflammation and oxidative stress. A number of these issues are reviewed in Chapter 5 (anti-oxidant defense), Chapter 8 (oxidative stress), Chapter 12 (cell proliferation) and Chapter 6 (genotoxicity).

The fiber story continues in the form of recent biopersistence studies with pure chrysotile, showing it to indeed have a very short half-life in animal studies (Bernstein, Rogers, and Smith 2003) and

in the rise in concern over carbon nanotubes, which can be very thin, very long, and very biopersistent (Donaldson et al. 2006) and which is discussed in Chapter 2 (mineralogy) and Chapter 22 (conceptual framework).

1.3 THE ROLE OF QUARTZ IN PARTICLE TOXICOLOGY

For a long time, the dust-induced disease that affected coal miners was thought to be silicosis. In the 1930s, the views of Haldane exerted great influence on this discussion. Haldane argued that silicosis, coal workers' pneumoconiosis, and bronchitis were clinically and pathologically distinct. Unfortunately, he also believed that pure coal dust was not harmful, in spite of some earlier studies on the effects of pure coal dust in coal trimmers (Collis and Gilchrist 1928), workers who are involved in the filling of bunkers and cargo holds in ships. This opinion remained in the United Kingdom and spread to the continent until the 1940s, when new reports showed that coal that was washed free of silica (Gough 1940; Hart and Aslett 1942) induced a "dust disease" that was pathologically different from silicosis, in coal trimmers and stevedores who leveled coal in the holds of ships. Interestingly, even after this epidemiological reappraisal, many epidemiological studies were conducted that concentrated on quartz content in relation to pathological category (King and Nagelschmidt 1945). Pursuing the quartz theme in coal workers' pneumoconiosis (CWP), 2% quartz mixed with anthracite failed to induce fibrosis by inhalation exposure in rats, and the same concentration of quartz alone was also without effect. In fact, after inhalation exposure in rats, clear signs of fibrosis were only seen when quartz was added to the coal dust to a level of 20% (Ross et al. 1962). Large-scale studies conducted in the course of ECSC medical programs (Table 1.1) were not able to show a consistent relation between quartz content of more than 40 respirable coal mine dusts, with *in vitro* toxicity, *in vivo* effects, or epidemiological outcome (Davis et al. 1982). Up to the 1990s, when exploration of the disease process of CWP proceeded at the molecular level, there appears to be only a quantitative difference between the response of key immunoinflammatory cells to quartz and coal mine dust (Gosset et al. 1991; Schins

TABLE 1.1
Major Differences between Exposure and Effects of Traditional (Coal) Mine Dust and Later Studies on Ambient Particulate Matter, Including Ultrafine Particles

	Mining Dusts (Coal, Asbestos)	Ambient PM/CDNP
Endpoints	Nonmalignant respiratory diseases (CWP, bronchitis, emphysema)	Mortality and exacerbations of existing diseases (asthma, cardiovascular, diabetes)
	Malignant respiratory (lung cancer, mesothelioma)	Lung cancer
Exposure routes	Inhalation	Inhalation
Target population	Workers (mining, shipyards)	World population
Target organs	Respiratory tract	Respiratory tract
		Heart
		Circulation, liver
Particle size	Respirable fraction <5 μm	Respirable (<2.5 μm) and ultrafine (<100 nm)
Exposure levels	Currently around 2 mg/m^3	Between 15 and 60 μg/m^3
	Historically up to 40 mg/m^3	
Indication of excess risk	For 35 yr, 1 mg/m^3	Increase of 10 μg/m^3, $PM_{2.5}$
	CWP (2–3%)	Daily mortality: 0.4–1.4%
	PMF (0.25%)	
	Bronchitis (50%)	Bronchitis: 5–25%

Note: CWP, coal workers' pneumoconiosis; PMF, progressive massive fibrosis; $PM_{2.5}$, Particulate matter <2.5 μm.

and Borm 1999), but many researchers still consider coal as an inert material mixed with an active principle, namely, quartz.

Notwithstanding the general reduction in mining in Western countries, research on quartz does continue. Many questions in coal-induced adverse effects still remain unanswered. Quartz has been classified as a human carcinogen (IARC 1997), but the question remains of whether mixed workplace dusts containing quartz should be considered as a carcinogen. Several research groups have addressed this question using different approaches. A series of studies has shown the variability of the natural quartz hazard with regard to inflammation and genotoxicity (Clouter et al. 2001; Bruch et al. 2004; Cakmak et al. 2004; Fubini et al. 2004). In another approach it was shown that coating the quartz surface with a small amount of aluminum, PVNO, or soluble matrix components for coal, reduced the ability of quartz to cause inflammation, DNA damage, hemolysis, and cell toxicity (Duffin et al. 2002; Schins et al. 2002; Albrecht et al. 2004).

The emphasis on quartz in the history of particle toxicology has left a legacy in that quartz remains the positive control of choice (DQ12 in Europe, Min-U-Sil® in the U.S.A.) for *in vitro* and *in vivo* studies. Quartz causes toxicity, inflammation and genotoxicity in the short- and long-term and so is used as a positive control, even in the nanoparticles era, since it can act as a check that toxicology assays are working and can detect a toxic particle.

The recognition that coalminers received very high exposures to relatively low toxicity dust raises the phenomenon of "rat lung overload." This phenomenon, seen at high exposure to low toxicity dusts in rats, is characterized by failed clearance, build up of dose, inflammation, and cancer. Although to be anticipated on the basis of Paracelsus' famous rubric, "everything is a poison—it is the dose that delineates the poison," this has been a concern for particle toxicologists using rats for hazard identification and risk assessment. Subsequently there has been much debate (Morrow 1988; Oberdörster 1992; Mauderly 1996). Originally the concept of "volumetric overload" dominated with the concept that the internal volume of macrophages occupied by particles had a inhibitory effect on phagocytosis (Morrow 1988, 1992). However, later work showed that surface area dose was the driver for onset of overload inflammation (Tran et al. 2000) and this helped to recognize how nanoparticles, with their huge surface area per unit volume, might act.

With regards to coal mine dust, in the human scenario, where there has been largest exposure to low toxicity dust, there is no evidence of lung cancer in coal miners and severe fibrosis is relatively rare. However, humans tend to interstitialize particles without much adverse effect (Nikula et al. 1997a, 1997b) which contrasts with rats, where interstitialization is linked to inflammation and adverse effects. There is general consensus that coal miners do not show the effects of rodent type overload (Kuempel et al. 2001) and that rats are unique, even amongst rodents, in showing a very extravagant pathogenic response to high lung burdens of low toxicity dust. This issue is intensively discussed in Chapter 21 on mathematical modeling.

1.4 FROM COAL MINE DUST AND ASBESTOS TO AMBIENT PARTICLES

Although some earlier well-known episodes of air pollution (Meuse Valley in 1930; London in 1952) were known to be associated with increased disease and mortality, it has taken many decades and series of epidemiological studies to convince both scientists and policymakers that, even nowadays, ambient particle exposures cause adverse effects leading to acute mortality. Dockery and coworkers in 1993 showed a relation between changes in acute mortality in the general population and variation in concentrations of PM in six different cities in the United States. This study has been reviewed and repeated, extended and updated (Samet et al. 2000), and followed by many others (Pope et al. 2004, review) but its initial findings have been confirmed in many different countries. From these studies it is estimated that per 10 $\mu g/m^3$ increase in the annual concentration of $PM_{2.5}$, mortality increases by 1.4%, while respiratory disease such as bronchitis or asthma exacerbations increase by as much as 4%. Based on the extent of these effects, particulate matter

still belongs to the priority topics identified by the EU and the U.S. Health Effects Institute (HEI), the WHO program, and the U.S. National Research Council (NRC 1998). Although epidemiological evidence suggests that it is the fine ($PM_{2.5}$) and even the ultrafine ($PM_{0.1}$) fraction that contains the toxic components, there is no general agreement on this issue (Oberdörster et al. 1994; Wichmann et al. 2000). The wide number of endpoints (from attacks of asthma to death) suggests that more than one component may be driving the health effects. However, compared to traditional research in particle toxicology, the exposures are much lower and the size of the particles is different. The current challenge is, therefore, to explain why exposures to PM_{10} (mass < 10 μm) typically as low as 40 $\mu g/m^3$, compared to 5–40 mg/m^3 in the coal mines, can cause acute death in those with asthma or cardiovascular diseases.

The PM research area is expanding rapidly with many changes compared to the former coal-driven particle research (Table 1.1). It is remarkable to have witnessed the change in focus from shift-type exposure in a specific underground occupation to the entire world population on a 24-hour-per-day basis. A major difference is the change in methodological endpoints, not confined to the lung but also focused on atherosclerosis, cardiovascular abnormalities, and recently effects on the brain (see Chapter 14, Chapter 15, and Chapter 19). A second fundamental change is the particle size of interest, with its impact on ambient measurements and experimental methods. Nanoparticles (< 100 nm) are the subjects of many toxicological investigations in animals and humans (Oberdörster et al. 2005; Donaldson et al. 2006; Nel et al. 2006, reviews) and have been shown to linked to adverse effects in epidemiology (Peters et al. 1997a; Wichmann et al. 2000). Animal studies have demonstrated that inflammation at "overload" is determined by the surface area dose of inhaled particles (Tran et al. 2000), which is greatly determined by the particle size. In addition to this effect, which is mainly caused by saturation of clearance, ambient fine and ultrafine particles, in view of their origins in fuel combustion, contain a large number of soluble metals and organics that have been associated with a variety of inflammatory responses (Chapter 8 and Chapter 11). Among the suggested mechanisms of activation, the production of intracellular oxidative stress and changes in Ca^{2+} levels leading to activation of transcription factors such as NF-κB, is the best described and elucidated in Chapter 9 through Chapter 11 of this book. The activation of NF-κB is well known to lead to transcription of a number of chemokines (IL-8), cytokines (TNF-α), and other enzymes (COX-2; inducible nitric oxide synthetase, iNOS) that are able to directly or indirectly enhance oxidative stress (Donaldson et al. 1998, review).

Funding strategies and criteria have changed dramatically since the heyday of the ECSC, to a molecular approach, and the global context of coal mining has also altered. Breakthroughs typically originate from links to other disciplines, such as cardiovascular pharmacology or immunology. The translocation of ultrafine particles into the bloodstream and their direct effect on heart and vessel wall is fascinating, and exposure *in vivo* to ambient particles does affect blood vessel contraction (Brook et al. 2002; Bagate et al. 2004; Mills et al. 2005). Whether this is a direct effect of translocated particles, or an indirect effect through inflammatory mediators released from the lung, is still open for research. One of the hot issues here is whether and how ultrafine particles can pass the lung barriers, as well as their general distribution and passage of membranes in the body. This issue is being discussed in a number of chapters in this book (Chapter 3, Chapter 7, Chapter 14, and Chapter 22).

Along with the evolution in our understanding of general disease, particle toxicology has benefited from the developments in molecular medicine. As the authors have described previously (Donaldson and Borm 2000), there has been a considerable change in the experimental approach taken by particle toxicologists. At the dawn of modern particle toxicology, in the late 1970s and early 1980s, cell death and injury were measured and we attempted to relate this to disease potential, probably reflecting what we *could* measure in those early days. The rise of inflammation as a key response to particle deposition in tissue and a process in particle effects has been inexorable and inflammation now lies at the very heart of our understanding of lung and systemic disease associated with particle exposure. As assays became available, we saw an increase in genotoxicity

studies and the important link between inflammation and genotoxicity was recognized and particles like asbestos and quartz were identified as both direct carcinogens and indirect carcinogens that acted through inflammation. As in all molecular medicine, there has been a huge concentration on the dysregulation of gene expression as a basis for disease, and this continues. Oxidative stress has emerged as the dominant paradigm for how particles initiate inflammation and genotoxicity, a stress further augmented by inflammatory cells releasing their arsenal of oxidants.

Together, the chapters in this book show a twenty-first century view of particle toxicology that has advanced from one where cell death and damage dominates pathological change only in the lungs, to a dynamic view where small particles, on top of effects in the lungs, may translocate to the blood and brain and reticuloendothelial system to exert effects. The gene lies firmly at the center of events and in sites where particles interact with cells, gradients of cytokines, and dynamic changes in antioxidant defense combine to modulate the expression of genes. Some of these gene products cause the antioxidant defenses to be enhanced, whilst others cause inflammatory cells to be recruited. Others stimulate mesenchymal cells to divide and lay down extracellular matrix. Inflammatory cells contribute further to the local cytokine "soup," which may travel systemically to affect the vascular bed and the vessel wall, especially atherogenesis, another inflammatory process. If particles reach the blood they may interact with platelets and the endothelium to enhance thrombosis, and even atherogenesis. Events in the vascular system may enhance atherothrombosis (Chapter 14), whilst in tissue inflammatory leukocytes may cause genetic damage to "innocent bystander" cells through release of their formidable arsenals of mediators and oxidants (Chapter 16). This proliferative and pro-mutagenic milieu is a fertile one for development of fibrotic lesions and clones of mutated cells that eventually culminate in cancer (see Chapter 4, Chapter 12, and Chapter 16). The particles themselves are phagocytosed, transported, undergo dissolution, and accumulate endogenous molecules. This dynamic view of cellular and molecular particle toxicology has been won by tremendous endeavor and insightful research across the world, which continues apace.

1.5 FROM ULTRAFINE PM TO NANOTECHNOLOGY

Translocation of nanoparticles, as mentioned earlier, is one of the tools being explored by pharmaceutical companies to deliver drugs in compartments such as the brain, which is otherwise hard to reach. Such medical applications are part of the possibilities generated by nanotechnology (Duncan 2003; Ferrari 2005). Nanotechnology is now considered to be one of the world's most promising new technologies, able to affect many industrial branches, just as coal mining did about a century ago (Borm 2002; Brune et al. 2006).

Nanotechnology is molecular manufacturing or, more simply, building things one atom or molecule at a time. Utilizing the chemical properties of atoms and molecules, nanotechnology proposes the construction of novel molecular devices possessing extraordinary properties. The trick is to manipulate atoms individually and place them exactly where needed to produce the desired structure. The major difference with current technology is that the starting points of conventional technology and nanotechnology are completely different. Instead of making things smaller by miniaturizing and using new materials, nanotechnology aims to build even smaller devices using atoms/molecules as a starting point. Technical applications now claimed feasible include catalysts, fuel cells, glues and paints, solar cells, smart drugs, and optical systems. Many researchers are tempted step beyond facts and step into visionary predictions, as did the late Dr. Richard Smalley, discoverer of buckyballs (Buckminster-fullerene, C60), and chairman of chemistry and head of the Nanotechnology Initiative at Rice University, who stated that "nanotechnology will reverse the harm done by the industrial revolution." In relation to coal dust-induced adverse health effects, it is hard to imagine how nanotechnology will be able to restore quality of life, or reverse the suffering and loss of productivity induced by respiratory diseases that afflicted thousands of coal miners.

Since only a few years toxicologists have become aware of the potential hazards of engineered nanomaterials (Borm 2002; Colvin 2003; Nel et al. 2006) especially if these will be used for medical applications (Buxton et al. 2003). Ultrafines, due to their small size, have a tremendous surface, which also makes them attractive for carrying drugs through the body. But again, the size of the surface and its chemical properties do determine their aptness for interaction with biological targets, and now many particles are produced, including dendrimers, polymers, quantum dots, magnetic carriers, and many others (Chapter 22 and Chapter 24). However, studies have demonstrated that even inert materials like gold and TiO_2 in nano size can become chemically active, due to the fact that the small size does not allow a surface of oxygen atoms alone (Jefferson and Tilley 1999). In other words, inert materials can become reactive just by making them smaller. Many nanoparticles are produced in emulsions or suspensions, and in order to maintain their single particle-based properties, are often surface-treated to prevent aggregation. As shown in earlier work with coal and quartz, these coatings may be even more important than the particle itself. However, recent work with ultrafine TiO_2, in which the surface was made hydrophobic by specific surface treatments, showed that this was less toxic and proinflammatory than its untreated ultrafine analogue (Oberdörster 2001; Höhr et al. 2002). However, every combination of surface coating and basic core material needs to be carefully evaluated in the future. The sources of evidence for the toxicity of nanoparticles (NP), originate from three classes of NP: bulk, combustion, and engineered nanoparticles (see also Chapter 22). The current discussion on engineered nanoparticles is mainly driven by data on combustion NP (diesel, ultrafines) and a small set of bulk NP (carbon blacks, TiO_2). However, that the current data set on engineered NP is growing and qualitative effects (inflammation, atherosclerosis, oxidative stress, Ca-transport, etc.) are also shown with various nano products, such as single wall nanotubes (SWNT). Some studies allow bridging of data, such as recent work (Radomksi et al. 2005) on platelet aggregation with different nanomaterials, but also including ambient PM samples. Since there is an overload of outstanding toxicology questions before we gain a conceptual understanding on nanomaterials, research, and regulation, the following issues need careful consideration:

1. Some effects of nanomaterials are probably the same qualitatively for engineered NP and others; this can be handled by checking the validity of current testing systems.
2. There is an urgent need to identify effects that are new for (engineered) NP and may occur in other populations and exposure situations than workers only.
3. Almost no data is available on ecotoxicity or ADME of NP, and this area should receive research priority.
4. When choices are to be made in testing and research, they should be driven by the application of the nanostructured materials.

1.6 IN CONCLUSION

Particle research has been historically closely connected to industrial activities or materials, such as coal, asbestos, manmade mineral fibers, and more recently, ambient particulate matter (PM) and nanostructured materials. Differences between historical and current research in particle toxicology include the exposure concentrations, particle size, target populations, endpoints, and length and extent of exposure. Inhaled particle effects are no longer confined to the lung, since particles are suggested to translocate to the blood while lung inflammation invokes systemic responses. Finally, the particle size and concentrations have both been reduced about 100-fold, from 2–5 to 20–50 mg/m^3, and from 1–2 μm to 20–100 nm (ultrafine), as domestic fuel burning has decreased and vehicle sources have increased and attention has moved from the coal mining industry to general environment. Exposures to nanoparticles in the nanotechnology sector, which continuously

produces new materials in the ultrafine range, are largely unknown. Although inhalation exposure is considered to be minimal in this technology, some particles are produced for consumer applications in household products, drugs, and foodstuffs. Clearly, particle toxicology is evolving with this trend and will have to develop new concepts of understanding particle actions, measuring, and testing particles and regulation.

All these observations underscore the importance of interdisciplinary research and exchange in the area of surface properties and activity of very small particles. Both epidemiological and toxicological studies have contributed to a body of evidence suggesting that coal, asbestos, and later ultrafine particles can induce or exaggerate a number of adverse effects. The last decade of PM research has shown a close collaboration between epidemiology and toxicology to solve important questions in this area. No doubt we are facing a next decade of challenging particle research driven by nanomaterials. Now the questions imposed on us by nanomaterials demand new collaborations with disciplines like chemistry, material sciences, and engineering. The formation of so called competence centers, or networks, where nanomaterials can be made and tested, will be vital for further development of sustainable nanomaterials. Both particle toxicology and nanotechnology will benefit from better knowledge generated in the twilight zone between materials and biological molecules.

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2 Mineralogy and Structure of Pathogenic Particles

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CONTENTS

2.1 INTRODUCTION

It is estimated that the element silicon makes up 27.7% of the earth's continental crust. The majority of this silicon is in the form of crystalline silicon dioxide (SiO_2) as the polymorph quartz, a well-established respiratory hazard (Rimala, Greenbergac, and William 2005). However, silicon is also present in numerous other minerals, and therefore, "silicates and non-silicates" have been used by mineralogists as a framework, further based on structure (ortho-, ring, chain, sheet, and tecto-), to describe all minerals (Deer, Howie, and Zussman 1966). This framework has been used in this chapter, but only minerals that are known or suspected to be respiratory hazards (Guthrie and Mossman 1993) are included (Figure 2.1 and Table 2.1). The chemistry and structure of minerals is complicated by the fact that many minerals exist in solid state series and in different shape "habits." For example, the chain silicate, amphibole, cummingtonite $(Mg,Fe^{+2})_7[Si_8O_{22}](OH)_2$-grunerite $(Fe^{+2},Mg)_7[Si_8O_{22}](OH)_2$ series. Grunerite is the name for the more iron-rich end-members, and is of significance here, because in its fibrous habit it is the mineral amosite; carcinogenic asbestos (Nolan, Langer, and Wilson 1999). In addition to the chemistry and habit, the formation conditions of the minerals can have bearings on the toxicity, e.g., SiO_2. The vast majority of crystalline SiO_2 occurs as the polymorph quartz, a mineral that usually forms at relatively low temperatures and high pressures. However, if SiO_2 forms at high temperatures and low pressures, such as near the surface in a volcanic dome, it forms the SiO_2 polymorph cristobalite. Concerns over the possible toxicity of volcanic ash particles have led to research which has shown

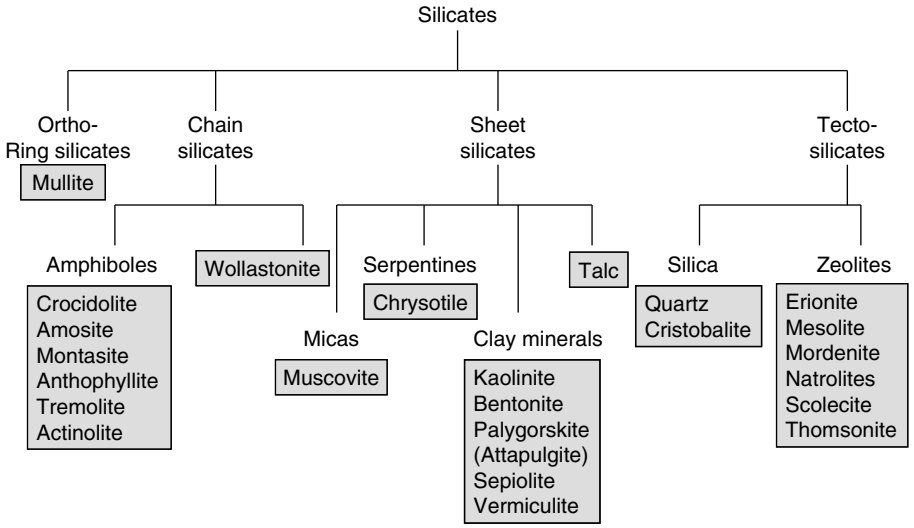

FIGURE 2.1 The distribution of some respiratory hazards within the silicates.

that respirable quartz and cristobalite have different bioreactivities in the lung (Housley et al. 2002; BéruBé et al. 2004; Forbes et al. 2004).

Minerals are the building blocks of rocks, therefore, on occasion we have to consider assemblages of minerals forming a rock type, which itself has been implicated in adverse respiratory health effects. An example of this would be "bauxite," the common name for aluminum ore derived from weathered igneous rocks. Bauxite consists of a mixture of aluminum hydroxide minerals, the most abundant of which is gibbsite, plus other major, minor, and trace minerals. There is an occupational respiratory disease unique to bauxite miners, "Shaver's Disease," but this has only been linked to the ore "bauxite," and not to any individual component mineral (Dinman 1988; Radon et al. 1999; Kraus et al. 2000). Another issue that arises when considering rock types as respiratory hazards is the matter of natural mineral contamination; vermiculite is a good example of this. Vermiculite is an important industrial and domestic material and is composed of clays that have been artificially expanded by heating. The problem is that the clay minerals, which are amenable to this process, can be naturally contaminated by potentially carcinogenic, asbestiform minerals, such as tremolite (McDonald, Harris, and Armstrong 2004). Serious precautions are therefore needed when using vermiculite, although it is probably not the vermiculite itself that is dangerous: rather, it is the trace amounts of contaminating tremolite that pose the hazard (Wright et al. 2002). In addition to recognized pathogenic minerals and rocks, this chapter includes descriptions of the chemistry and structure of pathogenic particles that, at first glance, would appear to be "non-mineral," yet upon close examination show a mineral component. An example of this would be "soot" from the combustion of fossil fuels. Soot is the most abundant component in urban $PM_{2.5}$ and has been linked to a number of respiratory issues, such as the increase in childhood asthma (Brauer et al. 2002; Nicolai et al. 2003). Examination of the carbon microspheres, that are the building blocks of soot particles, shows that they are largely composed of microcrystallites of the mineral graphite.

2.2 ORTHO- AND RING SILICATES

The orthosilicates, which include synthetic mullite, are based on SiO_4^{4-}, where the tetrahedral oxygen atoms are not shared with other tetrahedral. Also called nesosilicates, they are a diverse group of minerals. They tend to be rather hard and dense minerals with a generally poor cleavage. The ring silicates contain only three common species, and are isostructural with six-member rings

TABLE 2.1
Some Minerals and Particles and Their Known or Suspected Health Issues

Mineral	Some Known or Suspected Respiratory Health Issues
	Silicate Minerals
Synthetic mullite	Irritation of the respiratory system, silicotuberculosis
Crocidolite	Asbestosis, lung cancers, mesothelioma, pleural plaques, ferruginous bodies
Amosite	Asbestosis, lung cancers, mesothelioma, pleural plaques, ferruginous bodies
Montasite	Asbestosis, lung cancers, mesothelioma
Anthophyllite	Asbestosis, lung cancers, mesothelioma, plural calcification
Tremolite	Asbestosis, lung cancers, mesothelioma
Actinolite	Asbestosis, lung cancers, mesothelioma, non-malignant pleural lesions
Wollastonite	Lung fibrosis, respiratory morbidity, pulmonary toxicity
Chrysotile	Asbestosis, lung cancer, mesothelioma, pleural tumors
Talc	Talc pneumoconiosis (talcosis), pulmonary oedema, fibrotic pleural thickening
Muscovite	Pulmonary interstitial fibrosis, severe pneumoconosis
Kaolinite	Kaolin pneumoconiosis, simple and complicated Kaolinosis, COPD
Bentonite	Fuller's earth pneumoconiosis, "bentonite" granulomas, silicosis
Palygorskite (attapulgite)	Bronchoalveolar hyperplasia, alveolar tumors, mesothelioma
Sepiolite	Deterioration of lung function, co-carcinogen, fibrosis
Vermiculite	Natural asbestos contamination
Quartz	Fibrosis, silicosis, lung cancer
Tridymite	Fibrosis, silicosis
Cristobalite	Fibrosis, silicosis
Erionite	Lung cancer, mesothelioma, non-malignant fibrotic lung disease
Zeolites: mesolite, mordenite, natrolite, scolecite, thomsonite	Lung cancer
	Non-Silicate Minerals
Anatase	Chronic inflammation, lung tumors (rats), impaired pulmonary clearance
Apatite	Decrease in pulmonary function, hemolytic activity
Bauxite	Occupational pulmonary disability (Shaver's disease)
Fluorite	Bronchitis, silicosis, pulmonary lesions
Graphite	Graphite pneumoconiosis, focal emphysema, fibrosis and small fibrous nodules
Haematite	Siderosis
Siderite	Siderosis, "mottled" chest x-rays
	Rock Quarrying and Airborne Rock Dusts
Basalt	Pulmonary airway obstruction
Coal dust	Emphysema, coal-worker's pneumoconiosis
Dust storms	Desert lung syndrome
Pumice	Occupational silicosis, sclerosis of lymphatic glands, Liparitosis
Volcanic ash	Lymph node granuloma and delayed lung inflammation
	Urban, Rural, and Technogenic Particles
PM_{10}–$PM_{2.5}$, $PM_{2.5}$–$PM_{0.1}$	Asthma, pneumonia, bronchitis, heart failure
Nanoparticles	Asthma, pneumonia, bronchitis, heart failure
Fly ash	Asthma, pneumonia, bronchitis
Soot	Asthma, chronic bronchitis, radiological changes, skin cancer
Water-soluble component	Pulmonary inflammation, sudden cardiac death
Amorphous silicon dioxide	Inflammation, oedema, meta- and hyperplasia, fibrosis
Diatomaceous earth	Fibrosis, silicosis
Glass fiber/MMMF	Inflammation, occupational asthma, pleural plaques
Metals aerosols	Inflammation, lung cancer, metal fume fever

stacked on top of each other. Within the ortho- and ring silicates, a mineral of respiratory toxicological interest is synthetic (technogenic) mullite, a common refractory product (Carleton, Giere, and Lumpkin 2002). Particles of mullite are found in urban air, from sources such as coal-fired power stations (Giere, Carleton, and Lumpkin 2003). Mullite ($3Al_2O_3$ $2SiO_2$) occurs in most ceramic products containing alumina and silica. The mullite particles consist of needle-like interlocking crystals, growth of which is promoted by the presence of impurities. There have been concerns that workers in the ceramics industry exposed to mullite could suffer from irritation of the respiratory system (Fishman and Velichkovskii 2001; Fishman et al. 2001; Fishman 2003; Brown et al. 2005).

2.3 CHAIN SILICATES

The chain silicates are notable as they contain the carcinogenic minerals crocidolite and amosite. Chain silicates are a group of minerals with their tetrahedrons in single or multiple chains, with two oxygen atoms of each tetrahedron forming part of the adjoining tetrahedron. Amphiboles are a group of inosilicate minerals, containing hydroxyl (OH) groups, with double chains of aligned silicate tetrahedra. They exist in two different systems, orthorhombic (orthoamphibole) and monoclinic (clinoamphibole).

Crocidolite ($Na_2Fe_3^{+2}Fe_2^{+3}[Si_8O_{22}](OH)_2$) is commonly known as blue asbestos, and is the highly-fibrous form of riebeckite in the glaucophane-riebeckite group (Gibbons 2000). It has straight blue fibers that have a greater tensile strength than the most common asbestos chrysotile (sheet silicate), but less heat resistance. The fibers are prone to splintering when mechanically damaged. The size of the fibers plays an important role in asbestos-induced disease. The World Health Organization (WHO) defines fibers in the workplace as having a diameter of less than 3 μm and a length of more than 5 μm, with an aspect ratio of 1:3 or more; however, concerns have been raised about other issues such as biopersistence (Donaldson and Tran 2004). The fibers are believed to be hazardous to health since they are capable of entering and being deposited in the lungs, and have also a degree of migration capability within the lung (Stanton et al. 1981; Davis et al. 1986; Platek, Riley, and Simon 1992; Roller et al. 1996).

Amosite $(Fe^2+Mg)_7[Si_8O_{22}](OH)_2$ is the characteristic fibrous iron-rich form of cummingtonite–grunerite, and is commonly known as brown asbestos. It has straight, brittle fibers that are light gray to pale brown. It has good heat insulation properties and was commonly used in thermal systems insulation. Within the same series, the other asbestiform mineral of commercial importance is montasite, which is the softer and more magnesium-rich variety. Amosite is believed to have an equivalent health risk to crocidolite (Acheson et al. 1981; McDonald and McDonald 1996; Nolan, Langer, and Wilson 1999; Britton 2002).

Anthophyllite $Mg_7Si_8O_{22}(OH)_2$ is white to greenish-gray and is the magnesian end-member of the orthorhombic anthophyllite–gedrite series (Zeigler et al. 2002). Most anthophyllite crystals are prismatic or acicular. Fibers of anthophyllite are extremely flat and thin; the characteristic shape resembles that of a knife, and tends to be of generally uniform size. Tremolite and actinolite are asbestiform calcium amphiboles. Tremolite is a clinoamphibole and has the chemical formula, $Ca_2Mg_5Si_8O_{22}(OH)_2$. Actinolite $Ca_2(Mg,Fe)_5Si_8O_{22}(OH)_2$ has a similar composition, with iron replacing some magnesium. Wollastonite $CaSiO_3$ is a fairly common pyroxenoid inosilicate with industrial applications in ceramics and as filler. The mineral can be found as tabular crystals but is more commonly seen as lamellar radiating masses or fibrous aggregates. It is soluble in hydrochloric acid. Mechanical damage tends to result in elongate uneven splinters. All of the above fibrous minerals have recognized health issues [e.g., anthophyllite (Kiviluoto 1960; Dodson and Levin 2001; Dodson et al. 2005), tremolite (McConnell et al. 1983; Roggli et al. 2002; Luce et al. 2004), actinolite (Spurney et al. 1979; Metintas et al. 2005) and wollastonite (Huuskonen et al. 1983; Hanke et al. 1984; Wozniak et al. 1996; Tatrai et al. 2004; Maxim and McConnell 2005)].

2.4 SHEET SILICATES

The sheet silicates, or phyllosilicates, are composed of extending sheets of SiO_4 tetrahedra with the formula $(Si_2O_5)^{2-}$. Neighboring tetrahedra share the three oxygens of each tetrahedron. A second layer is formed from the apical oxygens that are attached to external ions. These external ions are in octahedral coordination. Different combinations of these two layers result in the different sheets silicates.

Chrysotile $Mg_3(Si_2O_5)(OH)_4$ is a generic term for undifferentiated, asbestiform, serpentine group species, consisting of a monoclinic mineral (clinochrysotile), and orthorhombic minerals (orthochrysotile and parachrysotile). Lizardite and antigorite are closely related serpentine group species (Kulagina and Pylev 1985). The most commonly used industrial asbestiform material, it consists of soft, silky white/green/yellow/gray bunches of flexible fibers. The fibers of chrysotile are formed by the crystalline sheet structure rolling into a scroll or coil form, giving a curly, tubular, hydrophilic fiber. This contrasts to the crystalline chain structure of the asbestiform amphiboles which exhibit a straight hydrophobic fiber. Health issues for the serpentines (chrysotile) are a well-researched issue (McDonald et al. 1993; Liddell, McDonald, and McDonald et al. 1997; Yano et al. 2001; Li et al. 2004).

Talc $Mg_3[Si_4O_{10}](OH)_2$ is a triclinic mineral composed of Si_2O_5 sheets with magnesium sandwiched between sheets in octahedral sites, and in tri-octahedral arrangement. Talc appears to be unable to form chemical-replacement series by accepting iron or aluminum into its structure. Rarely existing in an asbestiform habit, the major respiratory hazard posed by talc (Blejer and Arlon 1973; Wagner et al. 1977; Gibbs et al. 1992; Scancarello, Romeo, and Sartorelli 1996) is fine dust created by the milling to PM_{10} of soapstone and steatite. Commonly recognized as the primary ingredient in talcum powder, it is no longer recommended for dermal use (i.e., nappy powder), but it is still a significant industrial mineral. It is an important filler material for paints, rubber and insecticides (Di Lorenzo et al. 2003). In the food industry (Tomasini et al. 1988; Canessa et al. 1990), particularly in Asia, it is used as a mild abrasive in the polishing of cereal grains such as rice, potentially exposing workers handling the processed cereals to airborne talc (Breeling 1974).

Muscovite $KAl_3Si_3O_{10}(OH)_{1.8}F_{0.2}$ is the most common of the mica group minerals, and is typically found as massive crystalline "books" or in flaky grains. In the micaceous habit it has a platy texture with flexible plates. Muscovite has a sheet structure, of which basic units consist of two polymerized sheets of silica tetrahedrons positioned with the vertices of their tetrahedrons pointing toward each other and cross-linked with aluminum. Found in many different rock types, it is clear to milky-white with a pearly luster on cleavage faces, often with a sparkling appearance. Mica exposure is frequent in mines, mills, agriculture, construction, and industry and has been shown to induce pneumoconiosis (Landas and Schwartz 1991; Zinman et al. 2002). This health issue extends to people living around mica mines, as well as the workers in the associated mica-processing factories (Venter et al. 2004).

In the clay minerals group, the minerals associated with health concerns (Elmore 2003) include kaolinite, bentonite, palygorskite [attapulgite] (Huggins, Denny and Shell 1962; IARC 1980; Lipkin 1985), sepiolite (Baris, Sahin, and Erkan 1980) and vermiculite (Howard 2003). There is some debate on the actual health effects that can be attributed to the clay minerals themselves, since this group often has associated minerals with recognized adverse health effects. For example, kaolinite often has crystalline silica contamination, and vermiculite has both asbestos and crystalline silica as common contaminants.

Kaolinite $Al_2Si_2O_5(OH)_4$ is commonly known as kaolin or "China clay." The structure of kaolinite consists of tetrahedral silica sheets alternating with octahedral alumina sheets. The sheets are arranged so that the corners of the silica tetrahedrons form a common layer with the adjacent octahedral sheet. The charges within the structure are balanced, and analyses have shown that there is rarely substitution in the lattice. Visible crystals of kaolinite are extremely rare, with a typical grain size of 2–5 μm, with rare examples up to 1 mm across. When viewed under SEM,

the pseudohexagonal crystals have a platy appearance: both fibers and spheres have been observed under Scanning Electron Mircroscopy (SEM). "China clay" typically contains other minerals as contaminants, in particular quartz and muscovite, the former of which has known respiratory hazards (Lapenas et al. 1984; Wagner et al. 1986; Morgan et al. 1988; Gao et al. 2000). This is a result of the typical genesis of kaolinite from the weathering of feldspar in granite, where two other common granite components are the quartz and mica. The occupational respiratory disease associated with kaolinite has been variously named as complicated pneumoconiosis, kaolin pneumoconiosis, or kaolinosis (Mossman and Craighead 1982). Anecdotal evidence suggests that kaolinite workers in the enclosed spaces of the processing and storage buildings are more prone to illness than the workers out in the quarries. The symptoms are similar to silicosis; however, postmortem shows a profusion of small opalicities, and peribronchiolar nodules transversed by fibrous bands (Oldham 1983; Lapenas et al. 1984; Sheers 1989; Rundle, Sugar, and Ogle 1993; Parsons et al. 2003).

Bentonite is the common or generic name for "Wyoming" bentonite, swelling (sodium) bentonite, and non-swelling (calcium) bentonite. Montmorillinite clay ($(1/2Ca,Na)(Al,Mg,Fe)_4(Si,Al)_8O_{20}(OH)_4nH_2O$), which is part of the smectite group of clay minerals, is the main constituent of bentonite (Gibbs and Pooley 1994). The clay is formed by the alteration of volcanic ash, and where it shows a high absorbency capacity is commonly known as "Fuller's Earth." It is usually commercially seen in a finely ground powdered form, but is occasionally available as coarse particles, and has uses as diverse as cat litter to oil-well drilling mud. The potential of bentonite to cause fibrogenicity and granulomas (Boros and Warren 1973) in the lung has been investigated. In *in vitro* studies, bentonite showed a high membrane-damaging (lysis) potential, shown as hemolytic activity in human erythrocytes (Geh et al. 2005). Human epidemiological studies reviewing workers chest x-rays showed 44% silicosis in bentonite workers (Phibbs, Sundin, and Mitchell 1971). Other studies report seven months to eight years exposures to bentonite resulting in pneumoconiosis (Rombala and Guardascione 1955).

Palygorskite $(Mg, Al)_2Si_4O_{10}(OH)4H_2O$, also known as attapulgite, occurs as a fibrous chain-structure mineral in clay deposits in hydrothermal deposits, soils, and along faults. It is of commercial importance for a range of uses, typically as an absorbent. The fiber characteristics vary with the source, but fiber lengths in commercial samples are generally less than 5 μm. It can form matted masses that resemble woven cloth. Unlike most other clay minerals, palygorskite can form large crystals. The results of studies in animals suggest that carcinogenicity is dependent on the proportion of long fibers (>5 μm) in a given dust sample (Jaurand et al. 1987; Rodelsperger et al. 1987; Meranger and Davey 1989; Renier et al. 1989). In an inhalation study in rats, in which about 20% of the fibers were longer than 6 μm, bronchoalveolar hyperplasia and benign and malignant alveolar tumors and mesotheliomas were observed. Intratracheal instillation studies with palygorskite fibers in sheep and rat lungs demonstrated significant and sustained inflammatory and fibrogenic changes (Begin et al. 1987; Lemaire et al. 1989).

Sepiolite $Mg_2H_2(SiO_3)_3XH_2O$ is a similar clay mineral to palygorskite; it occurs as a fibrous chain-structure mineral in clays, with major commercial deposits in Spain. Sepiolite fiber lengths in commercial (e.g., animal/pet litter) samples are generally less than 5 μm. Inhalation/instillation into rat lungs of short and long fibers from different geological locations (i.e., Spain [short], Finland [long], China [long]) suggested that long sepiolite fibers, with slow elimination rates, were important factors for their adverse biological (fibrosis) reaction (Bellman, Muhle, and Ernst 1997). Sepiolite appears to be strongly hemolytic in many classic assays, and may act as a cocarcinogen (Denizeau et al. 1985). Lung function has been shown to deteriorate rapidly in workers who are occupationally exposed to the commercial dust (McConnochie et al. 1993).

Vermiculite $Mg_{1.8}Fe^{2+}{}_{0.9}Al_{4.3}SiO_{10}(OH)_24(H_2O)$ is the name given to hydrated laminar magnesium–aluminum–iron silicate, a mineral that resembles mica. Vermiculite deposits contain a range of other minerals that were formed at the same time. Of particular concern are vermiculite deposits from some sources that have been found to contain amphibole asbestiform minerals (Van Gosen et al.

2002; Gunter 2004; McDonald, Harris, and Armstrong 2004; Pfau et al. 2005), such as tremolite and actinolite. When subjected to high temperatures, vermiculite has the unusual property of exfoliating or "popping" into worm-like pieces (Latin *vermiculare*: to breed worms). The process occurs as a result of the rapid conversion of contained water to steam that mechanically separates the layers. The exfoliation is the basis for the commercial and domestic use of the mineral, the increase in bulk typically grades from $\times 8$ to $\times 12$, but can reach as high as $\times 30$. If the vermiculite contains asbestiform minerals, the exfoliation process releases fibers into the atmosphere. Vermiculite is used in the construction, agricultural, horticultural and industrial markets. The U.S. Environmental Protection Agency (EPA) has completed a study to evaluate the level of asbestos in domestic vermiculite attic insulation, and whether there is a risk to homeowners (USEPA 2005). There does not appear to be any indications that vermiculite itself is a respiratory hazard.

2.5 TECTO- (FRAMEWORK) SILICATES

Tectosilicates, formerly known as framework silicates, are minerals in which the silica tetrahedra share all four O^{2-} corners with adjacent tetrahedra. The result is a strong three-dimensional lattice. The large range of tectosilicates is a result of the partial substitution of Si by Al, balanced by cations such as K, Na, or Ca accommodated in the relatively open frameworks. The tectosilicates include many of the main rock-forming minerals, such as quartz and feldspars. Crystalline silica dioxide occurs in five different SiO_2 structures: quartz, cristobalite, coesite, tridymite, and stishovite. Three of the polymorphs: quartz, cristobalite, and tridymite have closely related temperature/pressure related crystallographic structures. Naturally-occurring coesite and stishovite are associated with meteorite impacts into silica dioxide-rich rocks, although coesite has also been found in kimberlite pipes in association with diamonds. From a human respiratory health perspective, only quartz, cristobalite, and tridymite are of importance (Fubini 1998; Occupational Safety & Health Administration [OSHA] 2005; Rimala, Greenbergac, and William 2005). The relative toxicities of quartz, cristobalite, and tridymite in the lung have been investigated by a number of workers, often generating different orders of toxicity. It is noteworthy that the OSHA permissible exposure limit values for cristobalite and tridymite are 0.05 mg/m^3, whereas quartz is 0.1 mg/m^3 (Castranova, Dalal, and Vallyathan 1997).

There are two dimorphs of quartz, α-quartz and β-quartz, with very similar structures. The determining factor for type of dimorph is temperature, with the boundary at 573°C. The structures are composed of networks of SiO_2 tetrahedra that are arranged in spiral chains (helices) around three- and six-fold screw axes. Alpha-quartz is trigonal and stable below 573°C. Above 573°C heat-induced agitation is sufficient to overcome a slight skewness in the structure and it converts to hexagonal β-quartz. The occupational development of acute silicosis and numerous different toxicological methods have shown that freshly-fractured silica dust is the most toxic (Castranova, Dalal, and Vallyathan 1997; Fubini 1998; Fubini and Hubbard, 2003; Rimala, Greenbergac, and William 2005). The consensus of opinion is that freshly cleaved crystal planes have surface properties that are more bioreactive with lung tissue, resulting in pulmonary disease. It is suggested that the silicon-based radicals ($\equiv$Si and Si–O$^{\cdot}$) created on the surface are of importance (Vallyathan et al. 1995; Fubini et al. 2001). This has been supported by electron spin resonance (ESR) spectra showing high values for freshly ground silica, followed by decay in the signal with time after grinding (Fubini et al. 1990). When shattered, the fresh crystal surfaces of the SiO_2 show greater or lesser degrees, and thicknesses of structural disorder (Baumann 1979). The size of the SiO_2 particles is also critical, as smaller masses have greater surface areas. Baumann (1979) calculated that powdered crystalline SiO_2 with a surface area of 11.8 m^2/gm had a perturbed surface of approximately 9%. In addition to the surface disorder (Altree-Williams et al. 1981), there is an internal component acting as potential boundaries between crystallites, potentially providing planes of weakness when the SiO_2 is powdered.

The monoclinic polymorph α-tridymite is stable at temperatures below 870°C (Smith 1998). At temperatures between 870°C and 1470°C it is hexagonal α-tridymite. Tridymite is only metastable at normal surface temperatures tending to alter, over thousands of years, to quartz. It retains its original, overall crystal morphology; thus much "tridymite" is really quartz pseudomorphs after tridymite. Tridymite was once considered to be rare, but it is now known that different volcanic rocks (e.g., in California, Colorado, and Mexico) can contain small to microscopic crystals of tridymite (USGS 2005). Nevertheless, it is still much less common than quartz or cristobalite and occupational exposures to tridymite could be expected in workers mining or processing powdered igneous rocks. Tridymite (and cristobalite) is produced in some industrial operations when alpha quartz or amorphous silica is heated (such as foundry processes, calcining of diatomaceous earth, brick and ceramics manufacturing, and silicon carbide production (NIOSH 1974; Weill, Jones, and Parkes 1994). Burning of agricultural waste or products such as rice hulls may also cause amorphous silica to become tridymite and cristobalite (Rabovsky 1995). For example, in Asian countries, the burning of rice husk ash (RHA), as a means to cover the demands for energy and silica resource (i.e., cement industry, lightweight construction products, abrasives, and absorbents), has been shown to generate cristobalite and tridymite (Shinohara and Kohyama 2004). The silica content in airborne dust for workers in RHA production factories, in power generation plants using rice hull, and engaged in farming operations that include the burning of rice husk, are now being controlled in the workplace due to the occurrence of pneumoconiosis in workers engaged in the packing and screening of RHA products (Liu, Liu, and Li 1996).

Cristobalite is the low pressure, high temperature SiO_2 polymorph, and is relatively abundant in volcanic rocks (Baxter et al. 1999). Cristobalite is only metastable at surface temperatures; the conversion to quartz is believed to occur exceedingly slowly. It is the presence of cristobalite in volcanic rocks that has prompted many of the concerns about the possible respiratory toxicity of volcanic ash (Baxter 1999; Baxter, Bernstein, and Buist 1986; Baxter et al. 1999). This is a subject of great interest, particularly after the May 18, 1980, eruption of Mount St. Helens (Baxter et al. 1981; Beck, Brain, and Bohannon 1981). There are also concerns for workers engaged in certain industries that can produce cristobalite as a by-product, such as glass manufacture (NIOSH 2002). Most cristobalite is believed to crystallize in a high temperature phase called β-cristobalite, with an isometric symmetry. It later cools, and the crystals convert to α-cristobalite. Alpha-cristobalite has an octahedron crystal form; however, when converted to α-cristobalite, the crystals retain the outward β-cristobalite form. As with quartz, it is the freshly-fractured faces of cristobalite that are of most respiratory concern.

Erionite is a fibrous zeolite (Gottardi and Galli 1985), with the approximate formula $(K_2, Na_2, Ca)_2Al_4Si_{14}O_{36}14H_2O$. It is a hydrated potassium sodium calcium aluminum silicate. Erionite forms wool-like, fibrous masses in the hollows of rhyolitic tuffs and in basalts. Approximately 40 natural zeolites have been identified, and they are noted for their very open crystalline lattices, with large internal surface areas. They are able to lose or gain water molecules, and exchange cations without major structural changes; this ability has led to many industrial applications, including use as "molecular sieves." Erionite is the most carcinogenic mineral fiber documented in man and in rodent inhalation studies. There is scientific consensus about the adverse effects of erionite in DNA strand breaks (Eborn and Aust 1995) or mesothelioma induction (Wagner et al. 1985). The considerable toxicity of erionite may be due to its fibrous nature and size, which ensures penetration into the lungs, and its surface chemistry, which promotes the formation of hydroxyl radicals (Hansen and Mossman 1987; Mossman and Sesko 1990; Fubini and Mollo 1995; Fubini, Mollo, and Giamello 1995; Fach et al. 2002).

Epidemiological studies in populated regions with high levels of naturally occurring erionite, (i.e., the Anatolian region of Turkey), have linked environmental exposure to erionite fibers with the development of malignant mesothelioma and non-malignant fibrotic lung disease (Baris et al. 1987; Artvinli and Baris 1979). The spectrum of cancers, fibrosis, and other pulmonary abnormalities associated with exposure to erionite is markedly similar to the range of health effects

described for occupational exposure to the amphibole asbestos, crocidolite, but the incidence of disease is increased dramatically. Human epidemiological studies have shown very high mortality from malignant mesothelioma in particular Turkish villages. This is an area where erionite is found in the local volcanic tuffs and the locals live in rock-built houses and caves (Lilis 1981; Artvinli and Baris 1982; Maltoni, Minardi, and Morisi 1982; Emri et al. 2002; Emri and Demir 2004). There is significant local airborne contamination from erionite, and the locals are exposed to the fibers from birth. Postmortem investigations found erionite fibers in lung tissue samples from cases of pleural mesothelioma. The inhabitants in contaminated villages had higher levels of ferruginous bodies than inhabitants of control villages (Dumortier et al. 2001). Several other natural zeolites, in addition to erionite, also can have a fibrous habit. Of particular health concern (i.e., "biologically active") are mesolite, $Na_2Ca_2Al_6Si_9O_{30}8H_2O$; mordenite, $(Ca,Na_2,K_2)Al_2Si_{10}O_{24}7(H_2O)$; natrolite, $Na_2Al_2Si_3O_{10}2H_2O$; paranatrolite, $Na_2Al_2Si_3O_{10}3H_2O$; tetranatrolite, $Na_2Al_2Si_3O_{10}2H_2O$; scolecite, $CaAl_2Si_3O_{10}3H_2O$: and thomsonite, $NaCa_2Al_5Si_5O_{20}6H_2O$ (Wright, Rom, and Moatmed 1983; Gottardi and Galli 1985; Fach et al. 2002).

2.6 NON SILICATES

The minerals anatase, rutile, and brookite are all naturally-occurring polymorphs with the same chemistry, TiO_2, but they have different structures. Anatase shares properties such as luster, hardness, and density with the other two polymorphs. It has a tetragonal symmetry, with the structure based on octahedrons of titanium oxide sharing four edges to produce a four-fold axis structure. Naturally-occurring anatase can be associated with quartz and is relatively rare in nature, occurring in cavities in schists, gneisses, granites, and other igneous rocks.

Titanium dioxide (TiO_2) is manufactured worldwide in large quantities for use in a wide range of applications. It is most widely used as a white pigment. This is due to its high refractive index and reflectance combined with its ease of dispersion in a variety of media and non-reactivity towards those media during processing and throughout product life. The two main processes for making TiO_2 pigments are the sulfate process and the chloride process. The sulfate process was the first to be developed on a commercial scale in Europe and the U.S., around 1930. It was the primary process until the early 1950s, when the chloride process was researched and developed. Currently, the chloride process accounts for $\sim$60% of the world's TiO_2 pigment production. Pure TiO_2 is extracted from its mineral feedstock by reaction with either sulfuric acid or chlorine, and then it is milled and treated to produce a range of products that are designed for specific end uses. The majority of TiO_2 products are based on the crystal- "type rutile, with a primary particle size range of 200–300 nm. In this context it is called "pigment grade." At this particle size, TiO_2 pigments offer maximum opacity, as well as impart whiteness and brightness to the paints, coatings, papers, and plastic products in which they are used. These TiO_2 pigments are also used in many white or colored products including foods, pharmaceuticals, cosmetics, ceramics, fibers, and rubber products, to mention only a few.

One of TiO_2 properties is its efficient absorption of ultraviolet light which makes it a very effective sunscreen for use in cosmetics. Usually its opacity is not required in this application, so very low particle size material (size 10–20 nm) is used and this is commonly called "ultrafine" or UF. The final product is of a particle size that could become airborne and inhaled. Titanium dioxide is highly insoluble, non-reactive with other materials, thermally stable, and non-flammable, which has led to it being considered to pose little risk to respiratory health. This is supported by the toxicological database on TiO_2 and the fact that it has been used traditionally for many years as a "negative control" dust in many *in vitro* and *in vivo* toxicological investigations. However, this view was challenged when lung tumors were found in the lungs of rats after lifetime exposure to very high concentrations of pigment grade TiO_2 (Lee, Trochimowicz, and Reinhardt 1985) and ultrafine TiO_2 (Bermudez et al. 2004; Hext, Tomenson, and Thompson 2005). In contrast,

no tumors were seen in similarly exposed mice and hamsters (Muhle et al. 1989; Warheit et al. 1997; Bermudez et al. 2002). These apparent species differences suggested that the experimentally-induced lung tumors were a rat-specific, threshold phenomenon, dependent upon lung overloading and accompanied by chronic inflammation to exert the observed tumorigenic response. The relevance of this phenomenon to human exposures remains questionable but, to date, epidemiological studies conducted do not suggest a carcinogenic effect of TiO_2 dust on the human lung (Hext, Tomenson, and Thompson 2005).

Apatite $Ca_5(PO_4)_3(F,OH,Cl)$ is a group of hexagonal minerals, usually subdivided into the three minerals; fluorapatite, chlorapatite, and hydroxylapatite. The fundamental unit of the apatites is the tetrahedral $(PO_4)^{3-}$ anionic group. The three types may partially replace each other, and it is hard to distinguish between them; therefore they are usually simply called "apatite." The most common of the three, by far, is fluorapatite. Apatite is the most common phosphate mineral, and is essential in the manufacture of phosphate-based fertilizers, and is important in the chemical and pharmaceutical industries. Concerns have been raised about the occupational respiratory hazards of phosphates (Sebastien et al. 1983) and apatite (Mikulski et al. 1994a). Epidemiological studies have been undertaken on the respiratory function of smoking and non-smoking workers exposed to apatite dust. It was concluded that occupational exposure to phosphorite and apatite dusts causes a decrease in pulmonary function in non-smoking workers (Mikulski et al. 1994b).

Aluminum ore, called bauxite, is usually formed in deeply weathered volcanic rocks, such as basalt. Bauxite is a heterogeneous material, mostly composed of several aluminum hydroxide minerals, plus varying amounts of silica, iron oxide, aluminosilicate, and other minor or trace minerals. The principal aluminum hydroxide minerals, $Al(OH)_3$ in bauxites are gibbsite and its polymorphs boehmite and diaspore. In gibbsite, the fundamental structure is a layer of aluminum ions, sandwiched between two sheets of tightly-packed hydroxy ions; only two of the three octahedrally-coordinated sites are occupied by cations. Aluminum ore dust, or bauxite dust inhalation, can result in "Shaver's Disease," corundum smelter's lung, bauxite lung, or bauxite smelters' disease (Dinman 1988; Radon et al. 1999; Kraus et al. 2000). This occupational disease in bauxite miners is a progressive form of pneumoconiosis caused by exposure to bauxite fumes which contain aluminum and silica particulates. Initially, the disease appears as alveolitis and then progresses to emphysema. Patients may develop pneumothorax (collapsed lung). It is typically seen in workers involved in the smelting of bauxite to produce corundum (crystalline form of aluminum oxide and one of the rock-forming minerals). Due to corundum's hardness, it is commonly used as an abrasive in machining, from huge machines to sandpaper. Emery is an impure and less abrasive variety.

The mineral calcium fluoride or fluorite, CaF_2, occurs as cubic crystals and cleavable masses. The calcium ions are arranged in a cubic lattice, with the fluorine ions at the center of smaller cubes derived by dividing the unit cell into eight cubes. When pure, it is colorless, however, impurities cause color, and some varieties fluoresce. It is common in limestone and dolomites, and has multiple uses in the fiberglass, ceramic, and glass industries. The respiratory hazards of fluorite are related to the fluorine and silica content. Acute inhalation has been linked to gastric, intestinal, circulatory, and nervous system problems. Chronic inhalation or ingestion can result in weight and appetite loss, anemia, and bone and teeth defects. The symptoms are therefore like those of fluorinosis, a disease associated with the ingestion of fluorine, usually in water or from contaminated land. It has been suggested that fluorite promotes silica fibrogenicity (pneumoconiosis) in the lungs (Xu et al. 1987). Fluorite miners have reported bronchitis, silicosis and pulmonary lesions (Xu et al. 1987).

The mineral graphite is a crystalline form of elemental carbon. Each carbon atom is covalently bonded, with bond length 1.42 Å, to three others in the same plane, with a bond angle of 120°. The carbon atoms thus form linked six-member rings to form flat or, occasionally, buckled planes. The sheets are usually stacked in an ABAB array, or less commonly in an ABCABC array. In comparison to the covalent bonds (1.42 Å) forming the sheets, the sheets are widely separated at a length

of 3.35 Å. The space between the sheets is known as the "van der Waals gap," due to the weak van der Waals forces attracting them together. Inhalation of dust containing graphite can cause lung disease in foundry workers and workers in graphite mines or mills. Mixed dust pneumoconiosis caused by long-term occupational exposure to graphite dust is a rare disease. Only a few cases of "graphite pneumoconiosis" have been reported in literature, and these were usually diagnosed postmortem (Domej et al. 2002). The characteristic symptom of graphite pneumoconiosis is non-asbestos ferruginous bodies based on a black graphite core (Mazzucchelli, Radelfinger, and Kraft 1996).

Siderite ($FeCO_3$) and hematite (Fe_2O_3) are both commercially-important iron ores. Siderite is rarely found in the pure $FeCO_3$ form, as it commonly substitutes Fe^{2+} with elements such as Mn or Mg. Siderite is slowly soluble in dilute HCl, leaving an iron oxide. When found as a common massive ore, hematite is known as "red hematite." Hematite has a structure consisting of layers of oxygen and iron ions perpendicular to the triad axis. As with siderite, hematite (Mossman and Craighead 1982) is rarely found in a pure form, with small amounts of MnO and FeO commonly present.

Siderosis is a "silicosis-like" occupational lung disease caused by exposure to iron carbonates and iron oxides. It is prevalent in hematite and other iron-ore miners (Chen et al. 1989, 1990) and workers in the iron and steel industries. Siderosis has similar diagnostic symptoms to simple pneumoconiosis, with the exception of a striking "mottled" appearance on chest x-rays. Post-mortem examination of siderosis patients is characterized by the deep brick-red staining of the lung tissue.

2.7 ROCK QUARRYING AND AIRBORNE ROCK DUSTS

Basalt is a hard, dark igneous (volcanic) rock with less than about 52 wt.% silica (SiO_2). It is the most common rock type in the earth's crust. Huge areas of lava called "flood basalts" are found on many continents, such as the Deccan Traps in India. Given its abundance, basalt quarries are commonplace worldwide, supplying rock for road surfacing, construction, and some industries. The common minerals in basalt include olivine $(Mg, Fe^{2+})_2SiO_4$, pyroxene [Ca, Na, Fe^{2+}, Mg, and others][Ch, Al, Fe^{3+}, Mn, and others](Si, Al)$_2O_6$, and plagioclase $(Na,Ca)Al_{1-2}Si_{3-2}O_8$, none of which is individually known to have respiratory toxicities. There are two respiratory health concerns associated with basalt. Firstly, finely-powdered quarried basalt for use in the ceramics industry, where an epidemiology study in India has shown 27% of the plant workers suffering from "basalt pneumoconiosis" (El Ghawabi et al. 1985). Secondly, a fibrous product spun out of molten basalt, basalt thin fiber (BTF) wool. Pure basalt wool is no longer crystalline basalt, but is actually non-crystalline glass with the same bulk chemistry as the original basalt. There are concerns about the similarity of the dimensions of basalt wool fibers to known carcinogens, such as asbestos, and the possibility that basalt wool could itself be a carcinogen (Adamis et al. 2001).

Coal dust consists of two main components: the organic particles and inorganic mineral grains. The coal itself is the organic component, and the different types of coal, depending upon the burial history and plant precursors, are classified as "macerals." For example, woody tissue-derived coal particles from a bituminous-rank coal would consist of the macerals "vitrinite." The rank of a coal relates to its burial history, which in turn determines the physicochemistry of the macerals. Low-rank coals are "lignites" or "brown coals"; medium-ranked coals are the "subbituminous" or "bituminous" coals; and high-ranked coals the "anthracites." During the "coalification" process during burial, as a result of temperature and pressure, the organic macerals become enriched in carbon, with the organic molecules becoming more cross-linked and refractory. The inorganic component of coal dust includes all the rock/mineral dusts that are associated with the coal and both mineral grains that were deposited at the same time as the coal, as well as minerals that formed in the coal subsequent to burial. Iron pyrite, FeS_2, is a common example of the latter type, and is the mineral that is mainly responsible for the emission of SO_2 from the burning of poor-quality coals.

The types and differing proportions of the different minerals to be found in "coal dust" thus relates to the geology of the coal mine or opencast (Figure 2.2a). Coal seams are found in sedimentary rocks, therefore are typically associated with sandstones, siltstones and shales (Figure 2.2b–Figure 2.2d). Some of the minerals found in these rock types, such as quartz and clay minerals, have recognized respiratory health effects. Therefore, when considering the possible toxic effects of "coal dust," we are in reality considering the toxicity of the mineral grains found in association with the actual coal (Jones et al. 2002). Occupational exposure to coal dust is a recognized cause of respiratory diseases such as emphysema and coal-worker's pneumoconiosis and is directly related to total exposure (Castronova and Vallyathan 2000). The highest incidence of respiratory disease is in underground coal-face miners. In general, anthracite coal mining has been associated with higher rates of pneumoconiosis than that found in bituminous miners (Ortmeyer, Baier, and Crawford 1973; Bennett et al. 1979). Anthracite coal mine dust contains more surface free radicals than

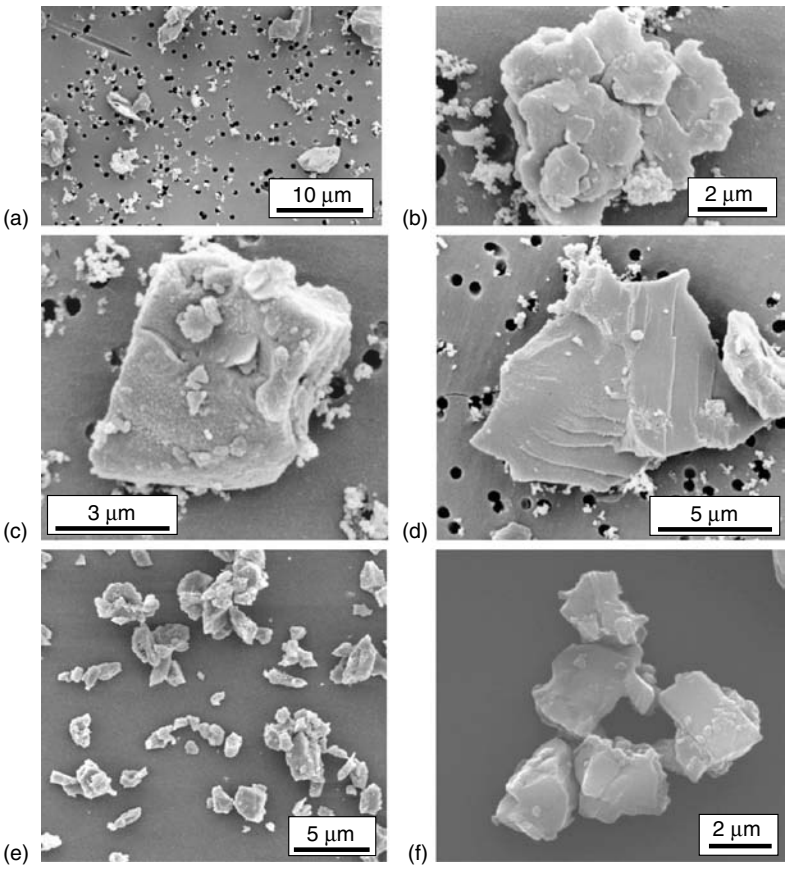

FIGURE 2.2 (a) Airborne mineral and soot particles from a coal open-cast pit collected on a polycarbonate filter. The minerals make up the bulk of the mass of the collection, however, the numbers of particles are dominated by soot particles. (b) Airborne clay mineral grain from a coal open-cast pit. (c) Airborne mineral grain from a coal open-cast coal pit. The grain shows poor cubic morphology. (d) Airborne mineral grain of microcrystalline SiO_2 from a coal open-cast coal pit. The grain shows conchoidal fracturing. (e) Airborne respirable volcanic ash particles from the Soufriere Hills volcano on the Island of Montserrat. The mineralogy cannot be determine from particle morphology, since no crystallinity can be seen. (f) Detail of respirable volcanic ash particles, the Soufriere Hills volcano, Montserrat.

bituminous coal, which may explain its higher cytotoxicity and pathogenicity (Dalal et al. 1990; Dalal et al. 1995). In addition, anthracite can have higher crystalline silica content than bituminous coal (Dalal et al. 1991). However, experimental evidence suggests that silica particles from bituminous mines may be coated with clay, rendering them less active (Wallace et al. 1994). Respirable coal mine dust has a relatively large surface area due to its small aerodynamic size and porous nature. Organic aromatic compounds present in the coal mine atmosphere, such as benzene, methylene, phenol, and phenanthrene, can be adsorbed onto the surface of coal mine dust and may affect its biologic activity.

Dust storms occur seasonally in many parts of the world, with the dust sourced from desert surfaces of loose dry sediment, that are typically receiving less than 250 mm annual rainfall and have little or no vegetation. The exposed surfaces can occur naturally, or as a result of poor agricultural practices. The "Dust Bowl" of the mid-West United States is a good example of the latter. The mineralogical makeup of dust depends on its source. Usually the source deposits consist of common minerals such as quartz, with associated clays and evaporites (salts), and the generated airborne dust reflects that composition. Silt and clay particles are commonly re-suspended from desert surfaces by wind. The larger particles (0.02 mm or larger) tend to remain suspended only minutes to hours, traveling at most a few hundred kilometers. The smaller particles can remain suspended in the atmosphere for weeks, traveling thousands of kilometers. Size fractionation of the different minerals, therefore, plays a part in the bulk mineralogy of the storms, with the smaller clay minerals an important component of the finer dusts. The respiratory health of desert inhabitants of the Saharan, Libyan, Negev, and Arabian deserts has been investigated (Nouh 1989; Hiyoshi et al. 2005). Long-term exposures can result in the development of a benign, non-progressive pneumoconiosis referred to as "Desert Lung Syndrome" (Nouh 1989). This condition is asymptomatic and does not appear to worsen with time. Researchers have suggested that the condition is benign because of the "age" of the mineral grains. Weathered dust particles have less reactive surfaces, whereas freshly fractured surfaces are more biologically reactive. A recent concern is the adverse health effects of a mixture of mineral dusts and urban PM_{10}, particularly in areas that experience both regular dust storms and high levels of man-made pollution. WHO estimates in Asia that outdoor air pollution causes more than 500,000 premature deaths a year.

Wind erosion in arid and semi-arid areas of middle and northwestern China forms the Asian Sand Dust (ASD) aerosol (Hiyoshi et al. 2005). This ASD spreads over large areas, including East China, the Korean Peninsula, and Japan. Sometimes the aerosol is transported across the Pacific Ocean to the United States (Duce et al. 1980; Husar et al. 2001; Kim, Han, and Park 2001). The sand dust aerosol originates in the sandstorms occurring in the Gobi Desert and the Ocher Plateau in spring. Both the daily observations and atmospheric concentrations of the dust aerosol have been increasing steadily in the eastern Asia region in recent years (Zhuang et al. 2001; Mori et al. 2003). ASD contains various chemical species such as sulfate or nitrate derived from alkaline soil which captures acid gases, such as sulfur oxides and nitrogen oxides (Choi et al. 2001). These gases are byproducts formed from coal and other fossil fuels combusted in industrialized eastern China. Recent epidemiologic studies have shown that ASD events are associated with an increase in daily mortality in Seoul, Korea (Kwon et al. 2002) and Taipei, Taiwan (Chen et al. 2004). ASD has also caused cardiovascular and respiratory problems in Seoul, Korea (Kwon et al. 2002).

Pumice is vesicular ejecta of feldspar-rich rhyolite lava that is poor in iron and magnesium and rich in silica. It is non-crystalline volcanic glass, with a general formula; $M_xO_y + SiO_2$, where M = Al, Ca, Mg and other metals with bound silica (SiO_2). Pumice has a low density and it can float on water, and is produced during eruptions of some stratovolcanoes, (e.g., Mount St. Helens and Montserrat). It occurs principally in Ethiopia, Germany, Hungary, Italy (Sicily, Lipari), Madagascar, Spain, and the United States. Some varieties, such as Lipari pumice, have a high content of total silica (71.2%–73.7%) and a fair amount of free silica (1.2%–5%).

Pumice tends to be soft, and has been used for building stone. It is also a mild abrasive, with some commercial uses and a household use in the removal of calloused skin from feet. Medical

concerns are centered on the major component of amorphous silicon dioxide. When used commercially, pumice is classified as a nuisance dust, with possible aggravation of pre-existing upper respiratory problems and lung disease. Pumice stone workers or miners are liable to occupational silicosis and sclerosis of the lymphatic glands. Extreme, non-occupational, exposures can cause lungs to be vulnerable to pneumoconiosis. Apart from the characteristic signs of silicosis observed in the lungs and sclerosis of the hilar lymphatic glands, the study of some fatal cases has revealed damage to various sections of the pulmonary arterial tree. Clinical examination has revealed respiratory disorders (emphysema and sometimes pleural damage), cardiovascular disorders (cor pulmonale) and renal disorders (albuminuria, haematuria, cylindruria), as well as signs of adrenal deficiency.

The description of pneumoconiosis due to amorphous silica is rare. One of these, named "liparitosis," is related to the inhalation of pumice powder extracted in the island of Lipari (Aeolian Archipelago, Sicily). Despite its low incidence due to localized exposure, liparitosis deserves a certain interest, as it can be considered representative of pneumoconiosis derived by amorphous silica compounds, including diatomite and artificial amorphous silica, the industrial manufacturing of which is extremely widespread. Liparitosis is characterized by a chronic evolution of 20–30 years. Clinically, it is almost silent, vaguely simulating a catarrhal bronchitis. From a radiological standpoint, it is described as the progression a fine reticulation to a later stage, characterized by mass-like fibrosis in the basal lung (Castronovo 1953; Mazziotti et al. 2004).

Volcanic ash is the fine airborne solid component of volcanic eruptions (Figure 2.2e and f). It is a material that can be produced in prodigious quantities, as large volcanic events can carpet vast areas in dust many meters thick. The respiratory dangers posed by volcanic dust include both during the eruption itself, as well as the ash "clean-up," sometimes long after the actual eruption has ceased. The nature of the hazard thus changes from an environmental exposure during the eruption, to an occupational exposure for those workers engaged in such tasks as sweeping ashfall off roofs. The composition, mineralogy, and structure of volcanic ash are determined by a very large range of factors, including the tectonic setting of the volcano and the nature of the eruption. Single volcanic events are capable of producing many different types of ash over the duration of the eruption. Most ash consists of a crystalline and an amorphous component. Concerns over the possible adverse respiratory effects of volcanic ash, have now focused on the crystalline SiO_2 content, a well-established respiratory hazard. Consequently, the eruption of the Soufrière Hills volcano on Montserrat has been extensively studied (Wilson et al. 2000; Horwell et al. 2001; Housely et al. 2002; Searl, Nicholl, and Baxter 2002; Horwell et al. 2003; BéruBé et al. 2004; Forbes et al. 2004; Lee and Richards 2004), and the varying percentage of cristobalite in the different ashes produced by this volcano established. The ash that contains the highest percentages of cristobalite is the "dome-collapse pyroclastic flow" ash. A volcanic dome forms when the magma moves up the volcanic conduit to the surface, and, relatively slowly, is extruded though a vent to form a pile or "dome." This dome is still very hot, typically around 800°C, and at surface pressures. With these high temperature and low pressure conditions, the SiO_2 polymorph cristobalite forms tiny crystals in open spaces (vugs) in the rock. Eventually the dome reaches an unstable size and collapses down the side of the volcano. This fast and dangerous collapse is called a "pyroclastic flow." The violent energy of the pyroclastic flow pulverizes the dome material into small fragments, releasing much of the cristobalite as fine airborne ash.

2.8 URBAN, RURAL, AND TECHNOGENIC PARTICLES

PM_{10} is defined as airborne particulate matter with a mean aerodynamic diameter of 10 microns or less; likewise $PM_{2.5}$ has a mean aerodynamic diameter of 2.5 μ or less. The PM_{10}–$PM_{2.5}$ is known as the "coarse" fraction, and the $PM_{2.5}$–$PM_{0.1}$ as the "fine" fraction and $PM_{0.1}$ is the "ultrafine" fraction. PM_{10} is highly heterogeneous, and as such, it is futile to try and define the mineralogy

or structure. However, broadly speaking, the composition of PM_{10} is controlled by factors such as weather, continental-scale influences, and regional and local influences. In urban and industrial areas, PM_{10} is dominated by road transport, industrial, and construction particles, whereas in rural areas, it is occasionally possible to recognize regional mineralogical signatures. Moreno et al. (2003) collected and analyzed crustally-derived (soil) particles from the Lizard Peninsula in Cornwall. The geology of the Lizard is unusual in the U.K. in that the serpentinite rocks contain minerals that are Mg- and Fe-rich, and these have altered in the soil to secondary minerals such as serpentine, talc, vermiculite, and tremolite. By comparison, with silicate minerals collected from London's air, a clear difference was recognized, and this enabled the "finger-printing" of local crustal PM_{10}.

Nanoparticles have been broadly defined as microscopic particles with dimensions less than 100 nm (Figure 2.2a, Figure 2.3b–Figure2.3d), however, "engineered" nanoparticles are more precisely defined as having one dimension less than 100 nm. Many nanoparticles are prone to rapid agglomeration, forming larger "particles" with dimensions much greater than 100 nm. These are termed "nanostructured particles," as long as their activity is governed by their nanoparticle components. For example, an agglomerate of TiO_2 nanoparticles forming a single "nanostructured particle" much larger than 100 nm in diameter, has significantly greater biological activity than a single crystal TiO_2 particle of the same diameter. With the development of nanotechnology, size effects of particles have gradually been considered to be important. Nanoparticles may be more toxic than larger particles of the same substance (Oberdörster et al. 2005a) because of their larger surface area, enhanced chemical reactivity, and easier penetration of cells. Nevertheless, several studies have shown that the cytotoxicity of nanosized TiO_2 was very low or negligible, as compared with other nanoparticles (Zhang et al. 1998; Peters et al. 2004; Yamamoto et al. 2004; Oberdörster, Oberdörster, Oberdörster 2005b), and the size was not the effective factor of cytotoxicity (Yamamoto et al. 2004). Probably the two nanoparticles of greatest interest to respiratory toxicologists are those composed of carbon (soot or carbon black) and TiO_2 (Humble et al. 2003). As previously described, nanoparticles (20 nm diameter) of TiO_2 will produce a persistently high inflammatory reaction in rat lungs, when compared with larger TiO_2 (250 nm diameter) particles (Oberdörster, Ferin, and Lehnert 1994; Oberdörster et al. 2005b).

Several methods, such as metallorganic and chemical vapor deposition, have been devised to produce TiO_2 nanoparticles of reproducible size. Given the bioreactivity of titanium, the expectation is that the surface of TiO_2 nanoparticles should be dominantly composed of oxygen atoms, but this is not supported by high-resolution transmission electron microscopy and the nature of the Fresnel fringe on the surface of the nanoparticles (Jefferson and Tilley 1999). The Fresnel fringe reflects the potential "drop off" at the crystal surface, and studies have indicated that nanoparticle surfaces contain titanium as well as oxygen. The implication of this is that the surface titanium has a distorted fivefold coordination, with resulting higher bioreactivity (Jefferson and Tilley 1999).

Fly ash is a generic term for particulate matter produced during combustion that primarily originates from mineral and metal contaminants in the organic fuels (Figure 2.3e–Figure2.3h). Some confusion exists between different scientific fields as to the definition of fly ash. This is a result of people describing materials as the end-product of combustion processes, rather than based on the composition of the materials themselves. For example, some archaeologists might include angular carbonaceous particles in their definition of fly ash, with this material actually representing charcoal or coke. The two main types of fly ash of interest to respiratory toxicologists are Residual Oil Fly Ash (ROFA) and solid fuel-combustion fly ash; these two materials are quite different. ROFA is a highly complex material containing transition metals, sulfates, and acids, incorporated with a resilient, particulate carbonaceous core (Ghio et al. 2002). Of particular interest and concern is the solubility, and therefore, bioavailability, of transition metals associated with these particles. The particulate carbonaceous core is effectively a soot particle, as described later in this section. Adverse respiratory health effects in humans due to occupational exposure to ROFA have been recorded (Hauser et al. 1995; Costa and Dreher 1997; Dreher et al. 1997; Kodavanti et al. 1997a; Kodavanti et al. 1997b; Kodavanti et al. 2000; Lewis et al. 2003; Antonini et al. 2004;

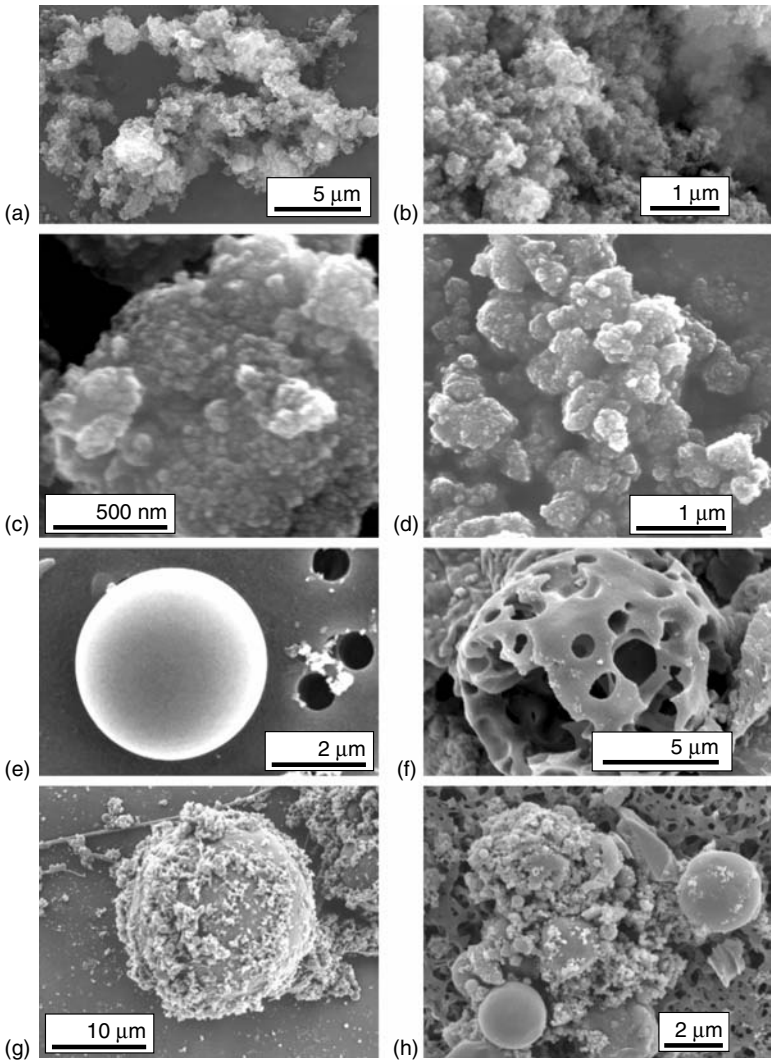

FIGURE 2.3 (a) Nickel oxide nanoparticles aggregated in nanostructured nickel oxide particles. (b) Silicon dioxide nanoparticles aggregated in nanostructured silicon dioxide particles. (c) Surface detail of nanostructured titanium dioxide particle. (d) Titanium dioxide nanoparticles aggregated in nanostructured titanium oxide particles. (e) Airborne iron microsphere collected in Port Talbot, South Wales. These are abundant in the local air, and with a mean diameter of 2 μm are almost all respirable. (f) A slightly damaged fly ash particle. This was collected in London during the 1950s, and was probably generated by the combustion of poor-quality coal for power and domestic use. (g) A sphere of fly ash that has been heavily coated in soot. (h) A composite particle consisting of metallic spheres, mineral grains, and soot.

Gardner et al. 2004; Roberts et al. 2004). ROFA is commonly used in studies evaluating the pulmonary responses to particulate matter exposure, partly due to the ease with which large homogeneous sample masses can be obtained from oil-fired power stations.

Fly ash produced by solid-fuel combustion is mainly sourced from mineral or metal contaminants in the fuel. Fly ash can thus be generated by the burning of coal, other fuel types (even municipal and commercial waste), and as a by-product of combustion-based industrial processes. Even though these combustion-using facilities usually extract the vast majority of airborne