5 Possible adverse health, environmental and safety impacts

5.1 Introduction

1 In Chapters 3 and 4 we have outlined the ways in which researchers and industry hope to exploit the unique properties of nanomaterials and the processes of nanomanufacturing for medical applications and to deliver environmental benefits. Current medical applications of nanotechnologies include anti-microbial wound dressings, and it is anticipated that future applications will include more durable and better prosthetics and new drug delivery mechanisms. Current research into applications of nanotechnology includes efforts to reduce the amount of solvents and other harmful chemicals in manufacturing, to improve energy efficiency and energy storage capabilities, and to remove persistent pollutants from soil and water supplies, all of which offer hope of benefiting the environment and increasing sustainability. In section 4.5 we highlighted the need to incorporate a life cycle assessment approach into the research and development of products and processes arising from nanotechnologies to ensure that they do not result in a net increase in resource use. In this chapter we consider potential adverse health, environmental and safety impacts of nanotechnologies.

2 Whereas the potential health and environmental benefits of nanotechnologies have been welcomed, concerns have been expressed that the very properties that are being exploited by researchers and industry (such as high surface reactivity and ability to cross cell membranes) might have negative health and environmental impacts and, particularly, that they might result in greater toxicity. The public who participated in the market research that we commissioned expressed worries about possible long-term side effects associated with medical applications and whether nanomaterials would be biodegradable. Analogies were made with plastics, which were once hailed as 'the future' but which have proved to have accompanying adverse effects on individuals and the environment (BMRB 2004).

3 Almost all the concerns expressed to us, in evidence and during our workshop on health and environmental impacts of nanotechnologies, related to the potential impacts of manufactured nanoparticles and nanotubes (in a free rather than fixed form) on the health and safety of humans, non-human biota and ecosystems. The fact that nanoparticles are on the same scale as cellular components and larger proteins has led to the suggestion that they might evade the natural defences of humans and other species and damage cells. It is important to set these concerns in context by noting that humans have always been exposed to some types of nanoparticles arising from natural sources such as atmospheric photochemistry and forest fires, and exposures to millions of pollutant nanoparticles per breath have been commonplace since the first use of fire.

4 Manufactured nanoparticles and nanotubes are important because they are among the first nanoscale technologies used in consumer products, but as Table 4.1 makes clear, the production rates of these materials is only a small fraction of the predicted potential for nanotechnologies. The IT industry also uses nanotechnologies, both in techniques used and the minimum feature size of devices; however, in contrast to manufactured nanoparticles and nanotubes, it does not present any unique hazards. There is an important distinction between applications that use nanoscalar active areas on larger objects (for example, nanometre-scale junction regions in transistors, which form part of a millimetre-sized chip and are therefore fixed), and chemicals or pharmaceuticals in which the nanometre-scale 'active area' is a discrete nanoparticle or nanotube. Although a computer chip with 100 million nanostructures presents a potential hazard for manufacture, disposal or recycling, these issues are related to the bulk materials, which make up the chips (for example, gallium), rather than to the nanostructures within them. Although nanoscience and nanotechnologies may involve individual scientists and other workers using or being exposed to a range of chemical reagents and physical processes that could imply harm to their health, such exposures to substances and materials other than nanoparticles are covered by existing understanding and regulation. They are not considered further in this report except in that they may be in the form of discrete particles incorporated into materials in the nanometre size range.

5.2 Assessing and controlling risk

5 The general approach to assessing and controlling risk involves identification of hazard (the potential of the substance in question to cause harm) and then a structured approach to determining the probability of exposure to the hazard and the associated consequences. Risk is usually controlled in practice by reducing the probability of exposure, although the first principle of risk management is to substitute less hazardous for more hazardous substances where possible. An appreciation of hazard (for example, toxicity or likelihood of explosion) is required to determine to what extent exposure should be controlled. Risk is controlled by limiting release of the material to air or water, and/or by interrupting the pathways by which the substance reaches the receptor where it could cause harm (for example an organ in the body), making an understanding of exposure pathways and likely quantities essential to risk management. In any new technology, foresight of possible risks depends on a consideration of the life cycle of the material being produced. This involves understanding the processes and materials used in manufacture, the likely interactions between the product and individuals or the environment during its manufacture and useful life, and the methods

used in its eventual disposal. Some of the definitions used in this chapter are outlined in Box 5.1.

Box 5.1 Definitions

Hazard is defined as the potential to cause harm: hazard is typically assessed by toxicology, for example testing harmful potential on cultured cells or isolated organs (*in vitro*) or directly on laboratory animals or humans (*in vivo*). Another hazard is the potential for clouds of combustible nanoparticles to explode.

Exposure is the concentration of the substance in the relevant medium (air, food, water) multiplied by the duration of contact.

Dose is defined here as the amount of a substance that will reach a specific biological system, and is a function of the amount to which the individual is exposed, namely the exposure, taking account of the fact that a proportion is eliminated by the body's natural defences and does not reach the target organ.

Risk is a quantification of the likelihood of such harm occurring: risk is assessed from consideration of the likelihood of exposure, the dose and the inherent toxicity of the substance to which people or other organisms may be exposed. Sometimes, in the case of materials to which exposure has already occurred, risk may be measured directly by the techniques of epidemiology.

6 Manufactured nanoparticles might be used in products where they are not fixed (such as sunscreens), be used to form composites from which they might later be released, be formed during the self-assembly of nanomaterials (again from which they might later be released), or be created if nanomaterials are damaged or break down. For physical harm to occur, humans or other organisms must come into contact with the materials or be involved in the processes in such a way that the material contacts or enters the body and takes part in reactions with cells, leading to tissue-damaging reactions. Any such damage might be anticipated if the material has toxic properties and reaches the target organ in sufficient dose (defined in Box 5.1). Some of the possible routes by which exposure might occur now and in the future after release of a nanoparticle are illustrated in Figure 5.1. If the material is released into the air, it may be inhaled directly. This is the dominant pathway for humans exposed to manufactured nanoparticles released in the workplace, and for all organisms exposed to nanoparticles from sources such as combustion. In addition to inhalation by air-breathing organisms, exposure to nanoparticles could occur from surface contact (for example in cosmetic skin preparations) or from ingestion (if nanoparticles are to be added to food or drink in the future). In the future, medicinal applications may result in particles being injected into the body. Other organisms such as bacteria and protozoa may take in nanoparticles through their cell membranes, and thus allow the particles to enter a biological food chain.

7 In this chapter we examine the possible hazards from nanoparticles before going on to consider the exposure pathways, any current exposure levels and how these might be managed to reduce the risk from manufactured nanoparticles and nanotubes. We address the important gaps in scientific understanding of possible interactions between nanoparticles, the environment and people, and outline the areas of research necessary to reduce these uncertainties. Ways in which regulation might be used to manage any risks presented by free nanoparticles or nanotubes are discussed in Chapter 8.

5.3 Human health

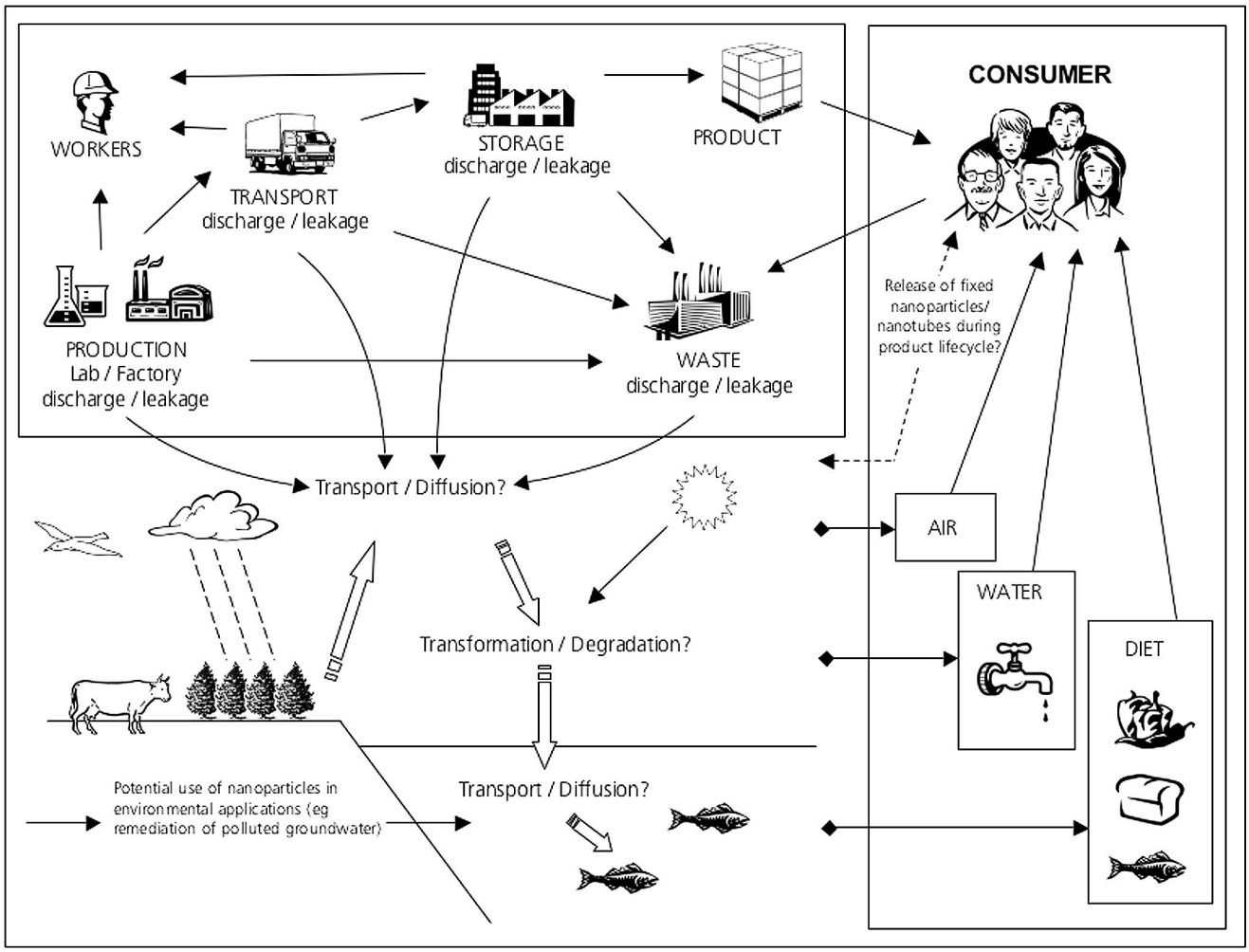
5.3.1 Understanding the toxicity of nanoparticles and fibres

8 To understand the potential risks to humans from nanoparticles, it is necessary first to consider briefly the body's defences against particles in general and the properties that particles require to overcome these defences. Throughout much of their evolutionary history, humans have been exposed to small particles, often in very high concentration, and the mechanisms evolved for defence against micro-organisms are also used to defend the body against such particles. Access to the human body can occur through the lungs, the skin or the intestinal tract. Each organ presents a barrier to penetration by micro-organisms or other particles. Nevertheless, despite the defence mechanisms outlined in Box 5.2, certain particles have proved to have toxic effects on humans, just as have certain micro-organisms. In general this is a consequence of properties that either allow them to evade or cause damage to defensive mechanisms. An understanding of these mechanisms is of importance to estimate the possible toxic effects of nanoparticles or nanotubes. Three types of particle in particular have provided relevant information: the minerals quartz and asbestos, and the particles associated with air pollution.

a) Evidence from exposure to quartz

9 Quartz is a mineral to which many millions of workers have been exposed, for example in mining and stone working. Exposure for a few years to micrometre-sized particles, in concentrations of the order of a milligram per cubic metre of air, leads to a potentially fatal form of lung fibrosis (Seaton 1995). Toxicological studies have shown that relatively low exposure to micrometre-sized particles of quartz causes severe lung

Figure 5.1 Some possible exposure routes for nanoparticles and nanotubes based on current and potential future applications. Very little is known about exposure routes for nanoparticles and nanotubes and this figure should be considered with this in mind (Adapted from National Institute for Resources and Environment, Japan http://www.nire.go.jp/eco_tec_e/hyouka_e.htm).



inflammation, cell death, fibrosis and tumours in rats (Vallyathan 1994). This has been demonstrated to be related to the surface of the quartz crystal, which is highly reactive and generates free radicals (reactive atoms or molecules), leading to oxidative damage to the defensive cells that take up the particles. It is likely that this surface activity is a fundamental aspect of the toxicity of particles but one that varies considerably between different types of particle. Other mineral particles encountered in industry, such as coal and various silicates, are less toxic but are still capable of causing similar diseases when inhaled in higher doses. It is now believed that inhaled particles in general, even when they have a low intrinsic toxicity to cells, may cause disease of the lungs if the dose is sufficiently high by overloading the lung defences, and that this property relates to the total surface area of the particles inhaled (Faux et al 2003). Thus studies of mineral particles have demonstrated that the toxic hazard is related to the surface area of inhaled particles and their surface activity. The risk relates to the dose inhaled.

b) Evidence from exposure to asbestos

10 The effects of asbestos have also been studied in great detail (Mossman et al 1990). Inhalation by workers of this natural fibrous mineral is known to cause several different diseases of the lung and its lining (the pleura), most of which prove fatal. Fibres are defined as particles with a length at least three times their diameter. Fibres narrower than about 3µm have aerodynamic properties that allow them to reach the gas-exchanging part of the lung when inhaled, whereas those longer than about 15µm are too long to be readily removed by macrophages (Figure 5.2). Once lodged in the deep lung, their toxicity depends upon an ability to initiate an inflammatory reaction, involving attraction of macrophages and other defensive cells, which, if sufficiently widespread, may eventually lead to scarring (asbestosis) and lung cancer. Over decades, migration of fibres through the lung to the pleura in sufficient numbers leads to the development of mesothelioma, a fatal tumour. Studies in rats have shown that the likelihood of a fibre, be it asbestos or some other natural or man-made fibre, to cause these

Box 5.2 Human defences against particles

Lungs

In the lung, small particles may be filtered out of the inhaled air by deposition on the airway wall and removal to the throat by the rhythmical beating action of microscopic protrusions (cilia) from the lining cells of the airways, or they may reach the gas-exchanging tissues and be engulfed by phagocytic cells called macrophages. These cells then carry the particles up the airways or through the lungs to lymphatic vessels and thence to lymph nodes. Both mechanisms tend to remove the particles from areas where they have the potential to cause harm and to neutralise their toxicity. However, an overwhelming dose may lead to excessive inflammation, scarring and destruction of lung tissue, as exemplified by bacterial pneumonia or industrial lung diseases such as asbestosis.

Skin

The skin is protected by a layer of dead cells (the epidermis or stratum corneum), covered by a hydrophobic (water-repelling) lipid layer. Beneath the epidermis is a layer of living cells supplied by nerves and blood vessels, the dermis. Within the dermis are glands that produce sweat and the protective secretion, sebum. The blood supply of the dermis allows recruitment of inflammatory cells when the skin is attacked by bacteria or otherwise damaged, enabling protective inflammation and tissue repair. Prolonged or repeated inflammation, such as may be induced by certain chemicals or by sunlight, may lead to skin damage and cancer. The epidermis is normally impermeable to particles and micro-organisms but is readily damaged (for example, by cuts and abrasions) or perforated (for example, by specialised insects or by therapeutic injections). Several skin diseases such as allergies can also impair its ability to withstand toxic agents.

Gut

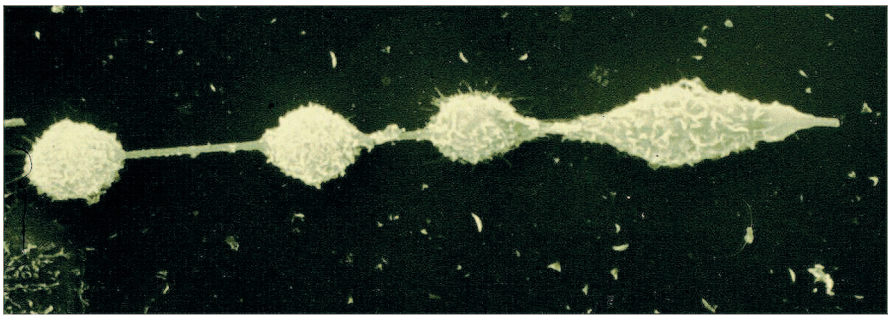
The epithelium of the gut differs from the other external epithelia in that its primary function is to allow absorption of substances into the body. However, unless diseased, it is impermeable to large molecules such as proteins (the largest of which are tens of nanometres in size), which it needs to break down before absorption, and to particles and micro-organisms. The high acidity of the stomach has an important microbicidal function, as well as a digestive one, and may dissolve some particles and affect toxins in various ways. The lower gut has a highly specialised secretory and absorptive epithelium that produces mucus and digestive enzymes and is richly supplied with blood and lymphatic vessels, allowing it to recruit defensive cells and remove penetrating micro-organisms if necessary. Research into better formulations for drug delivery has shown that some nanoparticles may be taken up by gut lymphatic vessels (Hussain et al 2001). Much disease of the gut relates to infections and to adverse reactions to foods. Environmental and occupational causes of diseases of the gut, other than these, are uncommon.

diseases depends critically on its solubility. Fibres that dissolve readily are likely to break into shorter particles that are easily removed by macrophages, and so are unlikely to persist long enough to cause such diseases (Mossman et al 1990). This has been supported by studies of human lungs, which have shown differential persistence of different fibre types in exposed workers with asbestos-related diseases (Wagner et al 1982). Asbestos is present in the fabric of many buildings and in cities, and all of us have some in our lungs. In contrast, those who develop asbestos-related diseases usually prove to have millions of fibres in every gram of lung tissue as a consequence of cumulative exposure to concentrations of several hundred fibres in every breath when they are exposed to the mineral at work over months or, more often, years (Wagner et al 1982). Thus, studies of asbestos and other fibres have shown that their toxicity depends on the two physical factors, length and diameter, and two chemical factors, surface activity and durability (ability to resist degradation). Again, the risk relates to the dose reaching the target organ.

c) Evidence from exposure to air pollution

11 Whereas studies of mineral dusts and asbestos have shown the importance of particle size, surface reactivity and dose in the causation of lung disease, the most direct evidence on nanoparticles comes from studies of air pollution. Any combustion process produces nanoparticles in vast numbers from condensation of gases. Initially only about 10nm in diameter, these rapidly coalesce to produce somewhat larger aggregates of up to about 100nm, which may remain suspended in the air for days or weeks (Figure 5.3). The sources of such combustion nanoparticles range from volcanic activity and forest fires, to the use of fires for heating and cooking, and more recently industrial and traffic pollution (Dennekamp et al 2002). Modern scientific interest in air pollution started after the disastrous London smog episode in December 1952, when some 4000 excess deaths occurred over a two-week period. Particle concentrations were as high as several milligrams per cubic metre, and most of these particles were in the nanometre size range. Reductions in pollution as a result of legislation to restrict coal burning have prevented such serious episodes from occurring

Figure 5.2 Four macrophages attempting to ingest an asbestos fibre (approximately 80µm long). (Reproduced by permission of Professor Ken Donaldson, University of Edinburgh).



subsequently in UK cities. Nevertheless, from the 1980s, a series of epidemiological studies has provided evidence that exposure to the particulate fraction of air pollution is associated with both heart and lung disease and is still responsible for measurable morbidity and mortality in urban areas as outlined in Box 5.3 (Brook et al 2004). This seems to be the case despite the fact that concentrations in western cities are now measured in concentrations of only a few tens of micrograms per cubic metre.

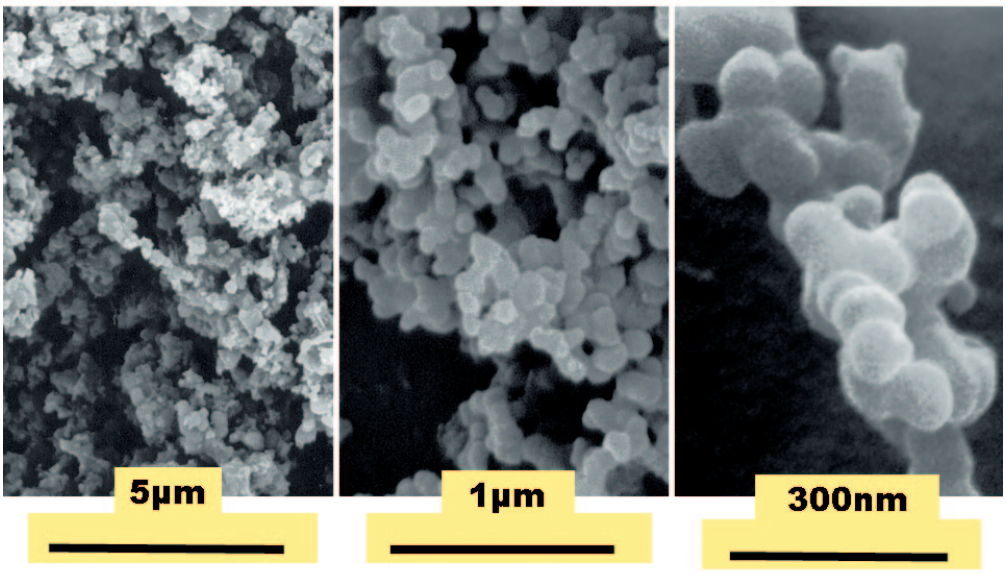
Box 5.3 Observed epidemiological associations between particulate air pollution and health

- Death from and exacerbation of heart disease in vulnerable people.
- Death from and exacerbation of chronic lung disease in vulnerable people.
- Exacerbations of asthma.
- Long-term increase in risk of death from heart attack and lung cancer.
- Possibly, precipitation of cot death and stroke in vulnerable individuals.

12 Air pollution is caused by a complex mix of particles and gases. However, there appear to be consistent associations between exposure to the particulate fraction and adverse health effects. In seeking to explain these, two difficult facts have had to be considered. First, the concentrations associated with measurable effects on health in populations are extraordinarily low – for example, rises of only 10µg/m^3 are consistently associated with an increase in cardiac deaths of about 1%. Secondly, the particles comprise chemicals generally believed to be non-toxic, mostly carbon and simple ammonium salts. It seemed unlikely that inhalation of less than a milligram of non-toxic particles over 24 hours (a human breathes about 20m^3 per day and urban concentrations average about 20–30µg/m^3) could cause a heart attack. Consideration of this problem led to the hypothesis that the adverse heart and lung effects are due to the action of the nanoparticulate component of the pollution on susceptible individuals, reflecting the point made above for quartz: that the total surface area and the surface activity hold the key to toxicity (Seaton et al 1995). Although the mass concentration of nanoparticles is low, it still amounts to some tens of thousands of nanoparticles per millilitre of urban particle counts (Figure 5.4). This concentration implies that one inhalation of 300ml will contain several million such particles, over half of which will be retained within the lungs. Activities such as cooking, driving in traffic or being in the presence of smokers entail breathing much higher concentrations. Since all are exposed yet few suffer adverse effects, it is generally believed that air pollution exerts its adverse effects on a minority of individuals who, because of prior illness, are particularly susceptible.

13 These studies of air pollution have therefore shown that although we are all exposed to very many, very small, apparently non-toxic particles on a regular basis, only relatively few of us succumb to their effects, but such effects may occur at very low mass concentrations. The concept that nanoparticles in air pollution might be responsible for the observed adverse health effects has promoted interest in their toxicology, and this interest is expanding rapidly. Review of *in vivo* animal studies supports the hypothesis that there may be a general effect of low-toxicity particles of all sizes that depends on the total surface area inhaled (Faux et al 2003); further investigation has shown that, weight for weight, finely divided particles of a material, such as titanium dioxide or carbon black, are more toxic than larger particles of the same material (Ferin et al 1990; Oberdörster 1996). This toxicity is largely explained by the presence of transition metals on the surfaces of some types of nanoparticle and their subsequent ability to promote release of free radicals in contact with body tissues (Donaldson et al 2001) However, other nanoparticles with no transition metals appear to achieve their effects by their large surface area and the ability of this surface to generate oxidative stress on cultured cells or isolated organs (*in vitro*) or directly on laboratory animals or humans (*in vivo*) by as yet

Figure 5.3 Soot nanoparticles viewed using Field Emission Scanning Electron Microscopy. (Reproduced by permission of Professor Roy Richards, University of Cardiff).



unknown mechanisms (Brown et al 2000). In both cases, nevertheless, the observed effects are related to the total surface area of inhaled particles and to the chemical reactivity of that surface, a sufficient dose to the lungs leading to inflammation and secondary effects on the blood that in turn lead to increased risk of lung and heart illness in susceptible individuals.

14 Owing to universal exposure to air pollution, and despite the defence mechanisms outlined in Box 5.2, many particles of all sizes do in fact enter the body mainly through the lungs, having been taken up by macrophages and transferred into the interstitial tissues. Some remain in the lung while some are removed through draining lymphatic vessels to lymph nodes and the blood stream. After death it is usually possible to find traces of the minerals to which workers have been exposed in their lungs (Seaton et al 1981), and very small amounts may be found in other tissues. Nanoparticles are probably removed from the lung more efficiently than somewhat larger ones, although inter-species differences are known to occur (Churg and Brauer 1997; Bermudez et al 2004). It is likely that a proportion of this removal is by the blood stream.

15 A few specifically designed epidemiological studies on human populations have investigated the cellular reactions demonstrated by *in vitro* and *in vivo* toxicology (Seaton et al 1999; Schwartz 2001). However, it is often difficult to attribute responsibility to one or other component of the air pollution (Seaton and Dennekamp 2003), and air pollution particles themselves are of differing chemistry and likely to include metallic atoms and molecules that will influence their toxicity. In general, epidemiological studies of air pollution point towards the finer particles rather than the coarser causing harm, although gases such as nitrogen oxides (which correlate closely with particle number) also show associations with several negative health impacts (Seaton and Dennekamp 2003).

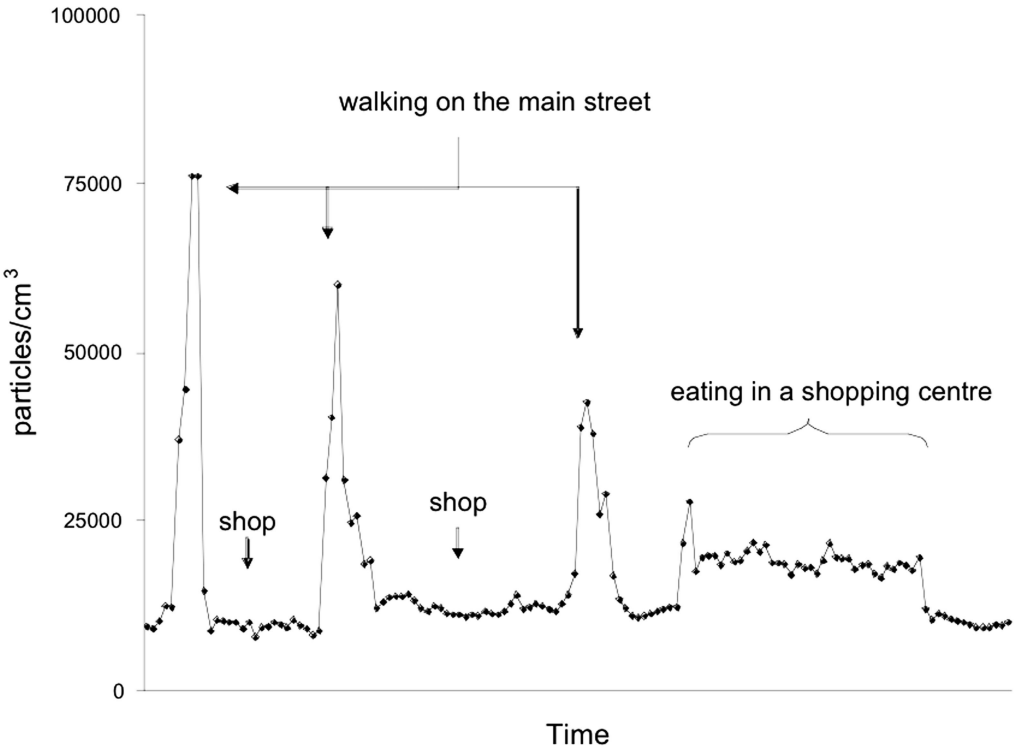
16 Observations linking air pollution episodes with cardiac responses (Peters et al 2000) and with changes in heart rhythm and sometimes blood pressure (Peters et al 1999) have led to suggestions that, as well as a humoral (or blood-borne) response, a short-term neural response to air pollution may occur. The mechanism for a response by the nervous system is not clear and is currently an area of active research. Nanoparticles would be a strong candidate (though not the only one: gases might have such an effect) for the role of initiator of the neural reflex; viruses may use nerves for transmission (Bodian and Howe 1941), and recent work has suggested that manufactured nanoparticles may penetrate and pass along nerve axons and into the brain (Oberdörster et al 2004b). There is also some evidence that metals characteristic of air pollutants may be found in the brains of urban dogs (Calderón-Garcidueñas et al 2003), and it is possible that transfer of particles along the nerves concerned with smell may provide a transport mechanism. More research on the neurotransmission of nanoparticles is needed.

17 The most significant finding from research into air pollution particles for the hazard of nanoparticles is that cells and organs may demonstrate toxic responses even to apparently non-toxic substances when they are exposed to a sufficient dose in the nanometre size range.

d) Evidence from medical applications of nanoparticles

18 Further information on the effects of nanoparticles on the human organism comes from the pharmaceutical

Figure 5.4 Exposure to particles over the course of a four hours spent in Aberdeen City centre. Measurements were taken using a PTrak continuous particle counter which counts all particles below 500nm, though in ambient air the very large majority are below 100nm. (Data collected by Martine Dennekamp, University of Aberdeen)



industry. For many years pharmaceutical scientists have studied the fate of nanometre-scale particles with the aim of developing novel drug delivery systems for pharmaceutical compounds (see section 3.5). These studies have been undertaken on spherical particles and have explored different routes of delivery including inhalation, ingestion, injection and transdermal delivery. Given the barriers to uptake of particles in the lungs, gut and skin, much of the knowledge on the fate of nanoparticles has been derived from studies of drug delivery by injection. It is known that after such administration the nanoparticles are taken up by macrophages in the liver and spleen. Ultimately, depending on their solubility and surface coating, they may be excreted by the kidneys (Borm and Kreyling 2004). In general, the options for removal of all foreign matter are excretion in urine or breath, through the gut by bile excretion, or in dead cells shed from the body. The use of surface coatings has enabled some particles to influence these disposal mechanisms and allowed them to be selectively deposited in particular organs or cells (Illum et al 1987). This suggests that surface coating might allow some nanoscale material to be directed to specific organs and that tests for toxicity need to take account of these coatings. It also implies the possibility that less desirable nanoparticles may penetrate into cells or cross natural barriers, such as those between the blood and the brain, that serve as important defences against harm.

5.3.2 Manufactured nanoparticles and nanotubes

19 In this section we consider the health impacts of manufactured nanoparticles and nanotubes, current and potential exposure routes and levels, and discuss ways of managing any potential risks.

20 The understanding derived from studies of air pollution, mineral dusts and pharmaceuticals has led to the general conclusion that the principal determinants of the toxicity of nanoparticles are:

- the total surface area presented to the target organ;
- the chemical reactivity of the surface (including any surface components such as transition metals and coatings), and particularly its ability to take part in reactions that release free radicals;
- the physical dimensions of the particle that allow it to penetrate to the organ or into cells or that prevent its removal;
- possibly, its solubility, in that soluble particles such as salts may disperse before initiating a toxic reaction.

a) Inhalation

21 The small size of nanoparticles ensures that a high proportion inhaled from the air reaches and is deposited in the deep lung. The size of nanoparticles appears to influence their uptake into cells. Specialised phagocytic cells such as tissue macrophages and leukocytes in the blood generally take up larger particles. This is a mechanism evolved in higher animals for removal of potentially harmful bacteria, and is analogous to the feeding method of unicellular organisms. Nanoparticles in contrast, because of their small size, may pass into cells directly through the cell membrane with the possibility of interfering with important cell functions such as motility and ability to remove bacteria (Renwick et al 2001).

22 Small size alone is not the critical factor in the toxicity of nanoparticles; the overall number and thus the total surface area (essentially the dose) are also important. Based on the evidence we have reviewed it follows that, although nanoparticles may imply a toxic threat because of their small size and therefore large surface area per unit mass, any toxicity would be expected to be dependent upon inhalation or absorption into the body of a very large number. For nanoparticles with low surface reactivity, potential toxicity to humans and, presumably, other animals, should be considered in relation to the likely dose and route of exposure. From the point of view of the lung, inhalation of small numbers of particles is unlikely to represent a significant risk. Inhalation of very large numbers, as may occur in a manufacturing process, should be controlled by regulation. For specific types of nanoparticle that may be expected to have a more reactive surface, perhaps because of a higher proportion or different combination of transition metals, greater caution would be advised and exposure should be minimised. Toxicological studies, both *in vitro* and *in vivo*, will be required for the investigation of any such substances to which people might be exposed.

23 Only a few types of manufactured nanoparticle, such as titanium dioxide, carbon black, zinc oxide and iron oxide are currently in industrial production (see Chapter 4). There is, however, a realistic prospect of industrial production of other nanoparticles for therapeutic or diagnostic use, often based on metals with chemical coatings that confer particular properties with respect to uptake into the body, across natural tissue barriers, and into cells (Borm and Kreyling 2004). There is also considerable interest in the possible production of nanotubes: some pilot manufacturing plants exist for CNTs, and nanotubes made of carbon and other elements are being extensively investigated in research laboratories. The greatest potential for exposure therefore over the next few years will be in the workplace, both in industry and in universities.

24 Workplace exposure will depend on production techniques (outlined in Chapter 4): for example, production and storage in liquid will reduce the risks of airborne exposure but fugitive emissions as vapour or wet aerosol may occur. Manufacturers must take account of the differences in toxic potential between larger and nano-sized particles and until the toxicology of the nanoparticles is better known, they should be assumed to be harmful and such workers seek protection by the usual methods of industrial hygiene, including provision of personal respiratory protection and appropriate hazard information, together with appropriate procedures for cleaning up accidental emissions and for making repairs to machinery. Several issues require further research. In particular, standard, validated methods of measurement and monitoring will be required to control airborne concentrations of nanoparticles in industry and academic laboratories, and the efficiency of various filter materials and respirator cartridges with respect to nanoparticles requires investigation. Toxicological research should be directed at assessing the hazard of new manufactured nanoparticles, particularly investigating the surface properties that alter toxicity.

25 As outlined in Chapter 3.2, nanotubes are of interest because they are mechanically strong, flexible and can conduct electricity. So far, most research has focused on CNTs but nanotubes made from other elements and molecules are also being developed. Perceived similarities with asbestos and other disease-causing fibres have led to concern about their safety. Technology exists that allows production of nanotubes that can have remarkable predicted dimensions of a few nanometres in diameter and micrometres in length (although currently they can only be produced as agglomerates, not as single nanotubes). These could represent a hazard because of their combination of fibrous shape and nanometre dimensions. It is also likely that such tubes are sufficiently robust to resist dissolution in the lung, and their dimensions suggest that they could reach the deep lung if inhaled as individual fibres. The presence of iron or other metals within them from its use as a catalyst in their production suggests that they may also have free-radical-releasing, pro-inflammatory properties. This has been borne out by one study that has investigated the effects of what must have been heavy doses in terms of numbers (60–240µg, dimensions unspecified) of single-wall nanotubes on cultured skin epithelial cells (Shvedova et al 2003). In this case the effects were probably due to the iron, and the tubes are likely to have been relatively short and clumped into masses. It is unlikely that such structures would remain as individual fibres in the air; rather, electrostatic forces probably cause them to clump into masses that are less easily inhaled to the deep lung. However, little is known of their aerodynamic properties and indeed whether they can be present in the air in sufficient numbers to constitute a risk.

26 If nanotubes were to intertwine and become airborne as 'ropes', these might pose a risk equivalent to a conventional fibre. If they combined as 'balls of wool' their aerodynamic diameter would be critical: greater than 10 µm diameter they would not be inhalable, whereas less than that they would act like larger particles. It is recognised, however, that one objective of current research is to find structures or coatings that enable the nanotubes to remain separate. In whatever final format, if they are inhalable, their toxicity is likely to be determined, at least in part, by their surface activity. The published mammalian studies relating to lung toxicity cannot be easily extrapolated, as of necessity the tubes were instilled (injected as a mass into the trachea rather than inhaled in a natural manner) as tangles rather than as individual fibres. The high masses instilled resulted in blockage of airways and intra-airway fibrosis - a not unexpected result in the circumstances (Maynard et al 2004). Preliminary studies in several workplaces suggest that single-wall nanotubes are difficult to disperse as an aerosol and tend to clump into large masses (Warheit et al 2004). Nevertheless, inhalation of small clumps may also imply problems for normal lung defences, with the possibility of them acting as large surface area, non-fibrous particles or being separated into single fibres by the action of lung surfactant.

27 If the barriers to producing single nanotubes (rather than clumps) are overcome, we would expect to see them used in many products such as electronic devices (as outlined in Chapters 3 and 4) and the potential exposure to manufacturing workers would increase. There are obvious difficulties in measuring aerosols of nanotubes against a background of normal laboratory or workplace air. The fact that they are currently difficult to disperse suggests that the escape of large numbers of individual fibres into the air is unlikely in normal processes. Given previous experience with asbestos, we believe that nanotubes deserve special toxicological attention; the types of studies that are required are listed in Box 5.4. The aim of such a programme would be to characterise as far as possible the potential for harm to occur by assessing possible human exposures in the laboratory and the workplace, and by performing simple tests of solubility and toxicity in vitro, assessing the validity of these tests by in vivo studies in small mammals. In the meantime, we believe that there is sufficient concern about possible hazards to those involved in the research and early industrial development of nanotubes to control their exposure. The role of regulation in controlling the exposure to nanoparticles and nanotubes in the workplace is discussed in Chapter 8.

Box 5.4 Assessment of likely risks to health of novel fibres such as nanotubes

Exposure studies
- Occupational hygiene study of production and use/disposal to determine the sizes and concentrations of fibres likely to be present in the workplace
- Are fibres longer than about 15 µm (preventing their removal by macropahges)?
- Can fibres reach the part of the lung responsible for gas-exchange (ie are they narrower than 3 µm)?

In vitro studies
- Are fibres durable (an indication that they might persist in the lung)?
- Do fibres kill cells, provoke inflammation and release free radicals?
- What is the effect of removal of metals on their toxicity?

Small mammal (in vivo) studies
- Do fibres persist in rat lung during following inhalation or instillation?
- Do fibres cause an inflammatory response following inhalation or instillation?
- Do fibres cause fibrosis and/or cancer after long-term inhalation?
- Do fibres cause mesothelioma (a cancer) after injection into rat pleura/peritoneum (membranes of the lung and abdominal cavity, respectively)?

b) Dermal contact

28 Currently, dermal exposure is limited to people applying skin preparations that use nanoparticles. Before and during this study, concerns were raised about the use of nanoparticles (particularly of titanium dioxide) for cosmetic purposes. Nanoparticles of titanium dioxide are used in some sunscreens, as they are transparent to visible light while acting as absorbers and reflectors of ultraviolet. Iron oxide is used as a base in some products, including lipsticks, although we understand that in Europe only sizes greater than 100 nm are used. It is clear that nanoparticles have different properties to the same chemical at a larger scale, and the implications of these different properties for long-term toxicity to the skin require rigorous investigation on a case-by-case basis.

29 Although the use of sunscreens reduces the risk of acute sunburn, the evidence that it prevents skin cancer in humans is far from established. There have even been suggestions that, perhaps by changing patterns of behaviour, the use of sunscreens may actually increase risks (IARC 2001). Some of the preparations used in sunscreens, including organic chemicals and particles, may themselves be photoactive in some conditions, so particular care is necessary in assessing their effects on the human skin. We have examined the concerns expressed to us that nanoparticles might penetrate the skin, that titanium dioxide is photoactive and that if it is

able to penetrate the skin it has the potential to generate free radicals that are known to cause damage to DNA. Limited toxicology so far on animal and human skin appears to indicate that the nanoparticles of titanium dioxide used currently in sunscreens do not penetrate beyond the epidermis (SCCNFP 2000) and that organic components of sunscreens are more likely to penetrate the skin than are the nanoparticles. The Scientific Committee on Cosmetic and Non-food Products (SCCNFP), which advises the European Commission, considered the safety of nanoparticles of titanium dioxide when used as a UV filter. They declared it safe for use at any size, uncoated or coated (SCCNFP 2000).

30 One of the concerns expressed to us was that the safety dossier submitted to the SCCNFP remains confidential to the industries supplying it, although the evidence supplied is referenced in the final opinion of the Committee. Although we recognise that industry has legitimate concerns about commercial confidentiality, we consider that this should not prevent data on the safety testing of cosmetic ingredients being accessible to the scientific community and other interested parties. We expect it to be possible for this to be done in a way that does not reveal proprietary information about the composition of individual products. Therefore, **we recommend that the terms of reference of scientific advisory committees (including the SCCNFP or its replacement) that consider the safety of ingredients that exploit new and emerging technologies like nanotechnologies, for which there is incomplete toxicological information in the peer-reviewed literature, should include the requirement for all relevant data related to safety assessments, and the methodologies used to obtain them, to be placed in the public domain**.

31 Cosmetics (including sunscreens) are intended for use on undamaged skin, and most skin penetration tests appear to have been designed with this in mind. Few reported studies indicate whether these particles penetrate skin that might have been damaged previously, for example by severe sunburn from sunlight exposure or by disease such as eczema. Uncoated nanoparticulate titanium dioxide is photoactive but the coatings used on titanium dioxide in sunscreens to prevent agglomeration also reduce the formation of free radicals (Bennat and Müller-Goymann 2000); so even if the titanium dioxide used in sunscreens were able to penetrate the skin it would probably not exacerbate free radical damage. Based on our concerns about sunscreens being used on damaged skin, our initial instinct was to recommend that all products containing sunscreens be regulated as medicines, as they are in the USA. However, we recognise that this poses challenges, including deciding how many and which types of product would fall into this category. We note that the UK has a total ban on the testing of cosmetic products and ingredients on animals and that the EU is in the process of moving incrementally towards a complete ban on all animal testing effective from 2013. Although tests on human skin and on cells are available, it is not clear that suitable non-animal models will be available for testing nanoparticles by 2013.

32 The SCCNFP has also considered the safety of nanoparticulate zinc oxide for use as a UV filter in cosmetic products and issued an opinion that they require more information from manufacturers to enable a proper safety evaluation (SCCNFP 2003a). In doing so they highlight evidence that zinc oxide (200nm and below – referred to as microfine) has phototoxic effects on cultured mammalian cells and their DNA *in vitro*. They recommend that the relevance of these findings be clarified by appropriate investigations *in vivo*. In addition, they commented on the lack of reliable data on the absorption through the skin of zinc oxide and noted that the potential for absorption by inhalation had not been considered (SCCNFP 2003a). The US Food and Drug Administration (FDA) has approved zinc oxide for use in sunscreens without restrictions on the size that can be used, although it is not clear if specific consideration was given to whether its properties were different at the nanoscale (FDA 1999). The uncertainties raised by SCCNFP about microfine zinc oxide as a UV filter are also relevant to its use in cosmetics and other skin preparations. In Europe, whereas all cosmetics must undergo a safety assessment by the manufacturer, only some categories of ingredients (such as UV filters) must be assessed by the SCCNFP before they can be approved for use.

33 The regulatory implications of our concerns relating to skin preparations containing free nanoparticles are addressed in Chapter 8.

c) Other exposure routes

34 Several therapeutic and investigative options for the use of nanoparticles are under development, with the broad aim of them being injectable and able to transport active chemicals to diseased cells. It is likely that such applications, when realised, will use relatively few particles that are biodegradable. As therapeutic substances, they should be subject to rigorous safety and toxicological testing before general release, and this testing will need to take account of their size as well as their chemistry. It is apparent that there has been little communication between pharmaceutical scientists investigating nanoparticles for their properties in evading cell defences to target disease and toxicologists investigating the properties of air pollution particles and the means by which they may cause adverse effects on organs distant from the lung. For example, nanoparticles are being investigated as carriers of proteins, such as antibodies, for pharmaceutical applications. This ability to conjugate implies that, once injected, a similar effect could occur with natural

proteins in vivo, interfering with the proteins' functions in the blood or within cells. It has been speculated that these interactions might alter a range of important cellular functions or indeed nullify the intended functions of the nanoparticles (Borm and Kreyling 2004). These possible hazards would most likely apply if nanoparticles intended for medical applications were injected or inhaled, and represent an area in which fundamental toxicological research is required.

35 There are two important implications of this lack of dialogue. First, research by pharmaceutical scientists will provide much useful information about the potential toxicity of nanoparticles being developed in other sectors and about means of reducing that toxicity. Secondly, when seeking novel applications of nanoparticles, pharmaceutical scientists need to be aware of the possible toxic properties of such particles, perhaps on organs or cells other than those targeted. It is important that the knowledge being gathered by each is shared with the other. Later in this chapter we consider how this might be facilitated.

5.4 Effects on the environment and other species

36 Although there is a body of literature about the human impacts of pollutant nanoparticles, research on the impacts of particulate air pollution on the natural environment and on non-human species within it has primarily been concerned with the impact of pollutant gases such as sulphur dioxide and ozone rather than particles. So with the exception of studies on some laboratory mammals related to investigation of human toxicology, there is no equivalent body of literature on non-human animals that can be used to consider the impacts of nanoparticles. Similarly, there is a dearth of evidence about effects of pollution nanoparticles, if any, on plants or micro-organisms.

37 We are only aware of one small published study of the impact of manufactured nanoparticles on non-human species (other than laboratory mammals). In the study in question, small numbers of juvenile largemouth bass (between four and nine fish in the treatment levels) were exposed to carbon 60 (C_{60}) nanoparticles (fullerenes) that had been treated to make them soluble (Oberdörster 2004a). A significant increase in lipid peroxidation (the oxidation of fats) was found in the brains of the fish after exposure for 48 hours to 0.5 parts per million (p.p.m.) C_{60}, but the increase was not significant at 1 p.p.m. The author noted clarification of the water in the treated fish tanks, suggesting a possible effect of the nanoparticles on micro-organisms. There is a need to follow up this pilot study with a larger and more detailed investigation.

38 It is plausible that soil or water organisms could take up manufactured nanoparticles escaping into the natural environment and that these particles could, depending on their surface activity, interfere with vital functions. The evidence that nanoparticles may inhibit motility and phagocytosis of macrophages, for example, suggests that similar effects might be expected on simple soil organisms. As with human toxicology, the dose to which the organisms are exposed would be expected to be critical in determining toxicity.

39 In common with other chemicals, nanoparticles may reach humans and other organisms by a wide variety of environmental routes. For example, organisms may ingest materials that have entered the water system or been deposited on vegetation. The criteria used to identify chemicals that have intrinsic properties that give cause for concern about their potential to damage the environment (or human health through the environment) are based on persistence, bioaccumulation and toxicity. The criteria used by the UK Chemicals Stakeholder Forum, for example, are outlined in Box 5.5. Chemicals that score highly according to all three criteria are of particular concern. Once inhaled or ingested, materials may enter the food chain, leading to the possibility of bioaccumulation and ingestion by organisms higher up the chain. Exposure by ingestion therefore depends on the persistence of the material (that is, its longevity in the environment) and its potential to accumulate, usually in lipids. Measures of persistence and bioaccumulation indicate when levels of a chemical are likely to build up in the environment and how difficult it will be to return concentrations to background levels if a problem is identified with the chemical. Bioaccumulation will depend on the surface properties of nanoparticles, which will determine whether they are likely to be taken up by the fatty tissues, bone or proteins in the body. For example, the C_{60} particles used in the study on largemouth bass (Oberdörster 2004a) were lipophilic, indicating that they could be taken up by fatty tissues. Persistence will depend on whether the material decomposes, for example by oxidation, and on whether the particles are modified in the environment, for example by agglomerating or adhering to other materials so that they lose the particular properties that could make them hazardous as nanomaterials.

Box 5.5 Criteria for concern of the UK Chemicals Stakeholder Forum

Persistence: Chemicals that are persistent are those that either take a long time to decay once they are released into the environment, or do not decay at all. The Forum classes a substance as persistent if it does not decay to half of its original quantity within two months (if in water) or six months (if in soil or sediment).

Bioaccumulation: Chemicals that are bioaccumulative have a strong tendency to be taken from solution (for example, in the stomach or from the blood of organisms that they enter) into the fatty tissues of the body where they remain. A substance is classed as bioaccumulative if, in tests to determine its attraction to fatty tissue over water, the substance favours fatty tissue in a ratio (quantity-wise) of 10,000 to 1 or more. Any substance that favours fatty tissue with a ratio of at least 100,000 to 1 is consequently considered as cause for extreme concern. Chemicals that accumulate in bone or bind to proteins are also of concern.

Toxicity: Chemicals that are toxic cause direct damage to organisms that are exposed to them. The Forum's criteria for toxicity generally follow those outlined in the EU Directive on dangerous substances (67/548/EEC). In addition to the Directive, a substance is classed as being of concern if it is fatal to at least 50% of waterborne organisms in a given sample, where the concentration of the substance is 0.1mg per litre or less.

Adapted from Chemicals Stakeholder Forum (2003)

40 For animals, simple tests for persistence and bioaccumulation are available (Royal Commission on Environmental Pollution 2003), and can be used for preliminary screening to identify chemicals whose risks may give cause for concern. In addition, there are numerous tests for toxicity. Whether these simple tests can be adapted for nanoparticles and nanotubes needs to be established and, if not, alternatives need to be developed. More generally, there is a need to establish appropriate methodologies for testing the toxicity of substances in nanoparticulate form in the context of both the environment and human health. Currently, almost nothing is known about the behaviour of nanoparticles in the environment (for example, whether they agglomerate and how this affects their toxicity); the only information on how they are transported through environmental media such as soil and water comes from initial studies on their potential for remediation, which indicate that nanoparticles of iron can travel with the groundwater over a distance of 20 metres and remain reactive for 4–8 weeks (Zhang 2003).

41 A current source of environmental exposure is in the waste streams from factories and research laboratories. Until more is known about the environmental impacts of nanoparticles and nanotubes, we are keen to manage any potential risk by avoiding their release into the environment as far as possible. Therefore, **we recommend that factories and research laboratories treat manufactured nanoparticles and nanotubes as if they were hazardous, and seek to reduce or remove them from waste streams.**

42 One of the difficulties in determining potential future exposure of the environment and humans to manufactured nanoparticles is the lack of information about both the extent to which they will be used in products and also the likelihood of such particles being released from nanomaterials such as composites in a form or quantity that might cause harm to humans or the environment. Although we expect that exposure from composites containing nanoparticles and nanotubes will be low – because they will typically make up a very small fraction of the final product and the functionality of the material will rely on them being retained – there is a need to test this assumption. We expect the ways of fixing nanoparticles and nanotubes will be proprietary. Therefore, **we recommend that, as an integral part of the innovation and design process of products and materials containing nanoparticles or nanotubes, industry should assess the risk of release of these components throughout the life cycle of the product and make this information available to the relevant regulatory authorities.**

43 Any widespread use of nanoparticles in products such as medicines (if the particles are excreted from the body rather than biodegraded) and cosmetics (that are washed off) will present a diffuse source of nanoparticles to the environment, for example through the sewage system. Whether this presents a risk to the environment will depend on the toxicity of nanoparticles to organisms, about which almost nothing is known, and the quantities that are discharged.

44 Perhaps the greatest potential source of concentrated environmental exposure in the near term comes from the application of nanoparticles to soil or waters for remediation (and possibly for soil stabilisation and to deliver fertilisers), as outlined in section 3.2. In some cases the nanoparticles used for remediation are confined in a matrix but, in pilot studies, slurries of iron nanoparticles have been pumped into contaminated groundwater in the USA (Zhang 2003). Given the many sites contaminated with chemicals and heavy metals, the potential for nanotechnologies to contribute to effective remediation is large. But this potential use also implies a question about eco-toxicity: what impact

might the high surface reactivity of nanoparticles that are being exploited for remediation have on plants, animals, microorganisms and ecosystem processes? It is of course possible that, in the concentrations used in remediation, any negative impacts on ecosystems will be outweighed by the benefits of the clean up of contaminated land and waters, but this needs to be evaluated by appropriate research and further pilot studies before deliberate release into the environment is allowed. In the UK, requests for use of nanoparticles in remediation of groundwater and other contaminated media are likely to be made to the Environment Agency. **We recommend that the use of free (that is, not fixed in a matrix) manufactured nanoparticles in environmental applications such as remediation be prohibited until appropriate research has been undertaken and it can be demonstrated that the potential benefits outweigh the potential risks.**

45 It has also been suggested to us that that nanoparticles might be used to increase the bioavailablity of pollutants, allowing them to be broken down by bacteria, or that they might be used to disperse and dilute pollutants. As with the example above, the very properties that researchers hope to exploit could potentially lead to unintended consequences for the environment, for example increased bioavailability of pollutants to plants and animals, or the transport of pollutants to sensitive ecosystems. This is clearly another area where more research is required alongside the development of these remediation systems.

5.5 Risk of Explosion

46 The explosion of dust clouds is a potential hazard in industries such as food production (sugar, flour, custard powder), animal feed production and places handling sawdust, many organic chemicals, plastics, metal powders and coal. The increased production of nanopowders such as metals has led to questions about whether there is a greater risk of explosion in the clouds of these nanopowders that might form during their production, transport or storage. Any dry, fine and combustible powder poses an explosion or fire risk, either through spontaneous combustion or ignition. The increased surface area of nanoparticles might mean that they would be more likely to become self-charged, and be more easily ignited. In addition, because of their small size, nanoparticles may persist for longer in the air, may be harder to detect and may be invisible to the naked eye, making crude detection difficult.

47 The UK Health and Safety Laboratory (HSL) has recently reviewed research in this area and found that although there is a body of literature about the explosion risk of micrometre-scale powders, no information exists on nanopowders (HSL 2004). Research on micrometre-scale powders reveals that explosion severity tends to increase with decreasing particle size, although for some substances this effect levels off. The report recognises that the changes in the physical and chemical properties of particles below 100nm mean that results from tests at the micrometre-scale cannot be extrapolated to the nanoscale, where the risk of explosion could be either greater or smaller. The HSL has identified the need for research to determine the explosion characteristics of a representative range of nanopowders; they believe that this research can be undertaken using standard apparatus and procedures already employed for assessing dust explosion hazards.

48 The risk of explosion can be avoided if combustible nanopowders are manufactured, handled and stored in liquid. By contrast, the drying of nanopowders in rotary driers is of particular concern. At present only a very few nanopowders are produced in the type of quantities that might present a dust explosion hazard (for example, carbon black). Other than these, specialist nanoparticles are currently produced or used in very small quantities (that is, grams) and do not pose this particular hazard. Until the explosion hazard has been properly evaluated, this potential risk can be managed by avoiding large quantities of combustible nanoparticles becoming airborne.

5.6 Addressing the knowledge gaps

49 Given the relatively small amounts of manufactured nanoparticles being produced, it is perhaps not surprising that there is a lack of information about their health, safety and environmental impacts. At present we have to rely by analogy on research results from air pollution and occupational research, the budget for which in the UK is very limited. Some research on the toxicity of new nanoparticles is underway, particularly in the USA (Service 2004). For example, the National Institute for Occupational Safety and Health in the USA is about to undertake a 5-year study into the toxicity and health risks associated with occupational nanoparticle and nanotube exposure, and is developing a dedicated centre to coordinate activities. Some work is also being funded by the European Commission.

50 With the exception of the research into air pollution by the Department of Health (DH) and the Department for Environment Food and Rural Affairs (DEFRA), no coordinated programme of research into the health and environmental risks of nanomaterials is being undertaken in the UK. We are pleased to hear that the UK research councils have committed to work together to address the issues raised in our report, and note that the Engineering and Physical Sciences Research Council (EPSRC) is assembling two 'thematic networks' in the area of nanosafety (House of Commons 2004b). In addition, the environmental impact of nanotechnologies is now on the agenda for the Environmental Funders'

Forum, which brings together the UK's major public sector sponsors of environmental science (including the research councils, DEFRA and the Environment Agency). As nanotechnologies advance, so environmental and human health hazard and risks should be investigated in tandem, priority being given to categories of products either in or near to the market.

51 The capacity for particle toxicology in the UK, based as it was on the need to protect workers in heavy industries such as those concerned with coal, steel and asbestos, has declined with the reduction in numbers of workers employed in such industries. However, a recent rise in interest in air pollution has allowed maintenance of a nucleus of expertise, particularly in Edinburgh and Cardiff. Traditionally, particle toxicologists have worked very closely with the relevant industries and the research councils. There is now an opportunity for a new collaboration between nanotechnologies, environmental science, pharmaceutical science and toxicology, building on the current expertise in air pollution and fibre research. Fundamental questions about the interactions of cells and their components and particle surfaces, and pragmatic questions about likely exposures and methods of their reduction, need to be addressed. We note the close relationship between toxic effects on cells such as macrophages derived from humans or other mammals and similar effects on organisms in the general environment. We also note the common interests of those concerned with research into possible beneficial effects of nanoparticles in the pharmaceutical industry and those concerned with toxicity. We believe that there is a strong case for a research dialogue between human toxicologists, pharmaceutical nanoscientists and eco-toxicologists.

52 A fundamental aspect of assessment of risk is the ability to quantify the hazard; this applies to all the above sections. Nanoparticles and nanotubes are too small to be measured by most standard instruments used, for example, in workplaces. Those instruments used for their quantification, electron microscopes and scanning mobility particle size analysers, are expensive and require a high level of expertise to use, although some cheaper, portable instruments are becoming available. Moreover, it is not known which physical property of nanoparticles is the one that correlates most closely with toxicity. The quantification of nanoparticles for regulatory purposes in mixtures such as cosmetics or in effluents would raise particular problems. There is an important need to develop, standardize and validate methods of measurement of nanoparticles and nanotubes in workplaces and the environment.

53 In Box 5.6, we summarise the research required to address some of the knowledge gaps highlighted in this chapter and to develop methodologies and instrumentation to support the regulation of production, use and disposal of nanoparticles (discussed further in section 8.4.3).

54 Much of the necessary research by its nature requires an interdisciplinary approach. Some of the relevant research should be done by Government agencies or through international collaborations, but it is important for the UK to have its own centre of expertise, which would maintain a database of information, become the centre of a network to disseminate this information, and act as a source of advice for industry and regulators.

55 **We recommend that Research Councils UK (RCUK) establish an interdisciplinary centre (probably comprising several existing research institutions) to research the toxicity, epidemiology, persistence and bioaccumulation of manufactured nanoparticles and nanotubes as well as their exposure pathways, and to develop methodologies and instrumentation for monitoring them in the built and natural environment.** A key role would be to liaise with regulators. **We recommend that the research centre maintain a database of its results and that it interact with those collecting similar information in Europe and internationally.** The remit of the research centre is summarized in Box 5.7.

56 Initially, RCUK will need to build expertise and collaborations in the areas outlined in Box 5.6, and it should work with the community to assemble an appropriate centre (along the lines of EPSRC quantum information processing Interdisciplinary Research Collaboration) rather than invite competitive bids. Its advisory board should include industrialists and regulators as well as scientists from the UK and overseas to ensure the wider relevance of the research programmes. Funding for the centre should keep pace with the development of manufactured nanoparticles. We estimate that funding at the rate of £5-6 M per annum for 10 years is needed to perform the tasks that we have outlined. Although core funding would need to be provided by the UK Government, we would expect to see the centre participating in European and internationally funded projects. As methodologies become established, the centre might become the recognized place for the testing of nanoparticles and nanotubes and develop a sustainable funding base within approximately 10 years. **Because it will not be possible for the research centre to encompass all aspects of research relevant to nanoparticles and nanotubes, we recommend that a proportion of its funding be allocated to research groups outside the centre to address areas identified by the advisory board as of importance and not covered within the centre.**

Box 5.6 Research areas to be addressed

- Development of suitable and practical methods for measurement of manufactured nanoparticles and nanotubes in the air and other media, including those properties most likely to reflect their toxicity such as surface area and potential to release free radicals.
- Investigation of methods of measuring the exposures of workers to manufactured nanoparticles and nanotubes in current laboratories and manufacturing processes.
- Development of international agreement on measurement standards.
- Establishment of protocols for investigating the long-term fate of nanoparticles as products containing them approach the market, to determine whether, how and to what extent they might come into contact with the natural environment.
- In conjunction with research on environmental remediation, develop an understanding of the transport and behaviour of nanoparticles and tubes in air, water and soil, including their interactions with other chemicals.
- Epidemiological investigation of the inter-relations of exposure and health outcomes in those industrial processes, such as welding, carbon black and titanium dioxide manufacture, where nanoparticle exposure has been known to have occurred for some time.
- Development of internationally agreed protocols and models for investigating the routes of exposure and toxicology to humans and non-human organisms of nanoparticles and nanotubes in the indoor and outdoor environment, including investigation of bioaccumulation. This would include an understanding of the impact of different sizes of nanoparticles and different types of coating.
- In collaboration with pharmaceutical nanoscientists and air pollution toxicologists, fundamental studies of the mechanisms of interaction of nanoparticles with cells and their components, particularly the effects on blood vessels, the skin, heart and the nervous system.
- Development of protocols for in vitro and in vivo toxicological studies of any new nanoparticles and nanotubes likely to go into large-scale production and which could impact people or the natural environment.
- Further investigation of the absorption through skin of different commercial nanoparticles used in dermal preparations, in particular any changes that may occur if the skin is damaged before application.
- Determination of the risk of explosion associated with a representative range of nanopowders (assuming funding has not already been received by HSL for this research).

Box 5.7 Remit of the proposed interdisciplinary research centre

- To undertake the research programmes outlined in Box 5.6.
- To act as the UK centre for advice on the potential health, safety and environmental impacts of nanomaterials.
- To hold regular dialogue meetings with appropriate regulators to exchange information on the requirements of regulators and research findings.
- To maintain a network bringing together those researching into:
    - epidemiology, toxicology, persistence, bioaccumulation, exposure pathways and measurement of manufactured nanoparticles and nanotubes;
    - medical applications of nanoparticles and nanotubes;
    - epidemiology, toxicity, exposure pathways and measurement of nanoparticles in air pollution.
- To maintain an accessible database of results from publicly funded research within the centre on the toxicity of nanoparticles and nanotubes, and to interact with those collecting similar information in Europe and internationally.

5.7 Conclusions

57 Many applications of nanotechnologies introduce no new health, environmental or safety aspects, for example where the nanotechnology is in the scale of a node on a computer chip or of nanometre thin films in data storage devices such as hard disks. Free particles in the nanometre size range do raise health, environmental and safety concerns and their toxicology cannot be inferred from that of particles of the same chemical at larger size. The difference comes largely from two size-dependent factors: the larger surface area of small particles compared with larger particles, given equal mass, and the probable ability of nanoparticles to penetrate cells more easily and in a different manner than larger ones. Exposure to natural and pollution nanoparticles in ambient and indoor air is universal, and most of the population and workers in many industries are exposed to high concentrations without significant harm. Nevertheless, in recent decades it has been suggested, though not proven, that such exposures may be responsible for the observed relationships between air pollution and several diseases, particularly of the heart and the lung, in susceptible individuals.

58 Toxicological investigations, based largely on low solubility, low surface-activity nanoparticles, have suggested that the ability of such particles to cause inflammation in the lung is a consequence of reactions

between cells and a large total particulate surface area (perhaps carrying reactive metals and other chemicals). Although it is very unlikely that new manufactured nanoparticles could be introduced into humans in sufficient doses to cause the effects associated with air pollution, nevertheless it is important that precautions are taken in the workplace in manufacturing and research laboratories to manage this potential risk by limiting exposure.

59 Moreover, it seems likely that the needs of industry will be met by development of a diverse range of nanoparticles with differing properties, and that these might lead to production of nanoparticles with surfaces that increase their reactivity and their ability to traverse cells, become blood-borne or cause injury to tissue. Therefore new nanoparticles that differ substantially from those with low solubility, low toxicity physico-chemistry should be treated with caution. If they are to be produced on a large scale they should be tested for their hazard and any likely human exposure assessed, so that risk can be minimised.

60 Exposure to fibres in industry, in the form of asbestos, is a well-recognised cause of serious illness, including cancer. The toxic properties of such fibres are dependent upon a diameter narrow enough to allow inhalation deep into the lung, a length that prevents their removal by macrophages, resistance to dissolution in tissue fluid, and a surface able to cause oxidative damage. However, the doses of asbestos associated with disease are substantial, of the order of several hundred per breath at work over months or years. Any new fibre with these properties would be expected to cause similar problems if inhaled in sufficient amounts to lead to similar lung burdens of long fibres. Carbon and other nanotubes have physical characteristics that raise the possibility of similar toxic properties, although preliminary studies suggest that they may not readily be able to escape into the air in fibrous form. Such materials require careful toxicological assessment and should be treated with particular caution in laboratories and industry.

61 Several nanoparticles are currently used in cosmetics and sunscreens. We believe the published evidence on toxic hazards from some such particles for skin penetration is incomplete, particularly in individuals using these preparations on skin that has been damaged by sun or by common diseases such as eczema. Further careful studies of skin penetration by nanoparticles being considered for use, and the propensity of such particles to potentiate free radical damage, are desirable.

62 The methods of quantifying nanoparticles and especially nanotubes pose serious problems at present. There is a need for more industrial hygiene and epidemiological evidence to guide regulation by different particle metrics; this requires research into appropriate instrumentation and standardisation of measurement.

63 Until research has been undertaken and published in the peer-reviewed literature, it is not possible to evaluate the potential environmental impact of nanoparticles and their behaviour in environmental media. **Until more is known about environmental impacts of nanoparticles and nanotubes, we recommend that the release of manufactured nanoparticles and nanotubes into the environment be avoided as far as possible.** In section 5.4 we make specific recommendations to reduce releases of nanoparticles and nanotubes in waste streams and those used for environmental applications in which nanoparticles are dispersed freely (for example, in remediation and soil stabilization).

64 Our conclusions have been based on incomplete information about the toxicology and epidemiology of nanoparticles and their behaviour in air, water and soil, including their explosion hazard. If nanotechnologies are to expand and nanomaterials become commonplace in the human and natural environment, it is important that research into health, safety and environmental impacts keeps pace with the predicted developments. In this chapter we recommend that RCUK establish an interdisciplinary centre (probably comprising several existing research institutions) to undertake research into the toxicity, epidemiology, biopersistence and bioaccumulation of manufactured nanoparticles, their exposure pathways, and methods and instrumentation for monitoring them in the environment. A key role would be to liaise with regulators. We recommend that the research centre maintain a database of its results and that it interact with those collecting similar information in Europe and internationally.

65 In this chapter we have identified several ways in which the risks of nanoparticles and nanotubes can be managed. In Chapter 8 we consider how this risk management can be incorporated into some of the relevant regulatory frameworks, such as those that relate to the safety of employees and consumers.