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Nanoparticles: An occupational hygiene review

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Nanoparticles: An occupational hygiene review

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Nanoparticles are the end products of a wide variety of physical, chemical and biological processes some of which are novel and radically different, others of which are quite commonplace. We have reviewed processes for the deliberate development and manufacture of nanoparticle products and have considered sources and routes of exposure, levels of exposure, numbers exposed, knowledge gaps and future trends. We conclude that all of the four main groups of nanoparticle production processes may potentially result in exposure by inhalation, dermal or ingestion routes and that little is known about current levels of exposure. Control approaches are available which should be effective for exposure by inhalation but this has not been demonstrated. Control approaches for dermal and ingestion exposure may not be as effective as they are for larger particles. Surface area is probably the best exposure metric for some but not necessarily all nanoparticles but there are no effective methods by which this can be measured in the workplace. Current knowledge is insufficient for risk assessment purposes. The number of workers who may be exposed to nanoparticles in the university sector and in emerging nanoparticle companies may be as high as 2000. Around 100,000 individuals may potentially be exposed to fine powders through various powder handling processes. It is not possible to say what proportion of these may be exposed to nanoparticles although it is likely to grow. More that 1,000,000 workers in the UK may be exposed to nanoparticles via incidental production in processes such as welding and refining.

In summary, we conclude that there is little evidence to suggest that the exposure of workers arising from the production of nanoparticles has been adequately assessed.

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EXECUTIVE SUMMARY

Nanotechnology is a broad interdisciplinary area of research, development and industrial activity which has been growing rapidly world wide for the past decade. It is a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic, processes, materials, applications and concepts in which the defining characteristic is one of size. Nanoparticles are the end products of a wide variety of physical, chemical and biological processes some of which are novel and radically different, others of which are quite commonplace. In this review we have focused on processes for the deliberate development and manufacture of nanoparticle products. Nanoparticle products include nanotubes, nanowires, quantum dots and “other” nanoparticles. We have reviewed and considered, for nanoparticle production processes;

- potential routes for human exposure;
- industrial sources of occupational exposure;
- level of exposure;
- means of, and effectiveness of control measures;
- potential numbers exposed;
- ease with which gaps in knowledge could be filled;
- trends in the (potential) use of nanotechnology;
- views as to the likely impact, of the implementation of the change from research use to full-scale industrial use.

The review comprised four main elements, a conventional scientific review, a web-based review, discussion with key individuals prominent in relation to scientific or industrial development of nanoparticles or their health effects or risk assessment and the experience and interpretation of the project team.

Conclusions

Based on our review of occupational hygiene aspects of nanoparticle production, we conclude that;

- There are four main groups of nanoparticle production processes (gas-phase, vapour deposition, colloidal and attrition) all of which may potentially result in exposure by inhalation, dermal or ingestion routes.

- From an occupational hygiene perspective, the processes are not dissimilar to existing chemical production processes.

- Only gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis stage. All processes may give rise to exposure (by inhalation, dermal and ingestion) to agglomerated nanoparticles during recovery, powder handling and product processing.

- For exposure by inhalation, control approaches and methods are available which should be effective in nanoparticle processes.

- For dermal or ingestion exposure, control methods based on personal protective equipment may not be as effective as they are in existing processes.

- The most appropriate metric in most cases for assessment of inhalation exposure to nanoparticles is particle surface area. There are no effective methods currently available by which particle surface are can be assessed in the workplace.

- Current knowledge is inadequate for risk assessment purposes.

- No information has been identified about workers exposures to nanoparticles in the university/research sector or in the new nanoparticle particle companies in the UK. Only very limited information is available for existing chemical, pharmaceutical and refining companies. Information from other powder handling process indicates that exposures may be significant.

- Approximately 2000 people are currently employed in the university/research sectors and new nanoparticle companies in activities in which they may potentially be exposed to nanoparticles in some form. A maximum of 500 workers are considered to potentially exposed to nanoparticles through existing ultrafine, manufacturing processes, mostly the manufacture of carbon black. Around 100,000 individuals may potentially be exposed to fine powders through various powder handling processes, including the pharmaceutical industry. It is not possible to say what proportion of these may be exposed to nanoparticles. More that 1,000,000 workers in the UK may be exposed to nanoparticles via incidental production in processes such as welding and refining.

- The number of people in the university/research sector, and in new nanoparticle companies may double over the next five years. The proportion of those involved in existing chemical and pharmaceutical companies and in other powder handling activities who are exposed to nanoparticles is likely to increase.

In summary, we conclude that there is little evidence to suggest that the exposure of workers arising from the production of nanoparticles has been adequately assessed.

Knowledge gaps
Arising from the review we also identified key knowledge gaps and made recommendations as to how they may be filled. These are:

1: The nanoparticle nomenclature is not sufficiently well described or agreed
Currently there are no agreed definitions for nanoparticles, nanoparticle aerosols, or for the various types of nanoparticles which are produced. Definitions proposed need to define a size interval to take account of the distribution in sizes likely to be present, to consider whether the definition should be based on physical dimensions (e.g. length, diameter, surface area) or on some behavioural property such as diffusivity and take account of agglomerated aerosols. Progress on nomenclature issues is usually best achieved based on consensus. The planned workshop on nanoparticle health risks (organised by HSE and NIOSH) to be held in October 2004 will provide an ideal forum to discuss these issues.

2: There are no convenient methods by which exposures to nanoparticles in the workplace can be measured or assessed
For inhalation, the most appropriate metric for assessment of exposure to most nanoparticles is particle surface area. Currently there are no effective methods available by which particle surface area can be assessed in the workplace. There is a need for more research into the development of new improved methods, combinations and strategies to provide reliable assessments of exposure to nanoparticles and nanoparticle aerosols. Development of appropriate methods to evaluate dermal and ingestion exposure is also necessary. HSE should consider how best to promote the development of appropriate metrics and exposure assessment approaches.

3: Insufficient knowledge concerning nanoparticle exposure is available
Much more information is needed regarding the exposure of workers involved in the production of all of the various types of nanoparticles via all of the production processes. In the absences of suitable measurements systems, coherent approaches as described above should be adopted. At this stage there is insufficient evidence to judge whether exposure to the various forms of nanoparticles is occurring at significant levels in nanoparticle production processes. HSE should consider how to encourage such data to be collected.

4: The effectiveness of control approaches has not been evaluated
Better understanding is required relating to the effectiveness of control of nanoparticles. This will be better informed given the development of appropriate methods for assessment of exposure to nanoparticles and a better understanding on the levels of exposure which may be acceptable. This is true for both inhalation, dermal and ingestion risks. HSE should consider how to promote the evaluation of control approaches.

5: Knowledge concerning nanoparticle risks is inadequate for risk assessments
Current knowledge is inadequate for risk assessment. Risk assessment approaches will have to consider how best to use information which is currently available, and plan to collect new information. An effective strategy for collecting, storing and disseminating this information is also necessary. Development of appropriate databases, and other information resources which can be used to collect and disseminate information on studies to investigate exposure or toxicological assessment of nanoparticles is a key element in this. HSE should consider what it can do to collate and maintain and disseminate information relevant to nanoparticle risk issues.

1. INTRODUCTION

Nanotechnology involves the creation and/or manipulation of materials at the nanometre (nm) scale either by scaling up from single groups of atoms or by refining or reducing bulk materials. A nanometre is 1 x 10^{-9} m or one millionth of a millimetre. To give a sense of this scale, a human hair is of the order of 10,000 to 50,000 nm, a single red blood cell has a diameter of around 5000 nm, viruses typically have a maximum dimension of 10 to 100 nm and a DNA molecule has a diameter of 2 – 12 nm (www.nano.gov). The use of the term "nanotechnology" can be misleading since it is not a single technology or scientific discipline. Rather it is a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic, processes, materials, applications and concepts in which the defining characteristic is one of size.

Nanotechnology is a rapidly evolving and expanding discipline and has aroused growing media and public interest. Articles appear daily in the scientific and popular press and on a host of websites dedicated to the field. New companies, often spin outs from university research departments, are being formed and are finding no shortage of investors willing to back their ideas and products. New materials are being discovered or produced and astonishing claims are being made concerning their properties, behaviours and applications.

While much of the current "hype" is highly speculative, there is no doubt that worldwide, governments and major industrial companies are committing significant resources for research into the development of nanometre scale processes, materials and products. In Europe, the Sixth Framework Programme has nanotechnology as one of its seven main thematic programmes (www.cordis.lu). The programme, "*Nanotechnology and nanosciences, knowledge-based multifunctional materials and new production processes and devices*" has a budget of €1,300 million for the period 2002-2006 (http://www.cordis.lu/nmp/home.html). A similar large scale programme, the National Nanotechnology Initiative (NNI), is running in the USA with a budget of approximately $1,000 million for 2005 (http://www.nano.gov/). In the UK, the Department of Trade and Industry (DTI) has recently launched the "Micro and nanotechnology manufacturing initiative" with a budget of more than £90 million (http://www.dti.gov.uk/nanotechnology/).

Development of new nanomaterials is a major theme of all of these programmes. Ordinary materials such as carbon or silicon, when reduced to the nanoscale, often exhibit novel and unpredictable characteristics such as extraordinary strength, chemical reactivity, electrical conductivity, or other characteristics that the same material does not possess at the micro or macro-scale. A huge range of materials have already been produced including nanotubes, nanowires, fullerene derivatives (bucky balls), and other nanoscale materials.

Nanotechnologies are gaining in commercial application. Nanoscale materials are currently being used in electronic, magnetic and optoelectronic, biomedical, pharmaceutical, cosmetic, energy, catalytic and materials applications. Areas producing the greatest revenue for nanoparticles are reportedly chemical-mechanical polishing, magnetic recording tapes, sunscreens, automotive catalyst supports, bio-labelling, electro-conductive coatings and optical fibres (http://www.nano.gov/html/facts/appsprod.html). Further example applications may be found on the National Nanotechnology website at http://www.nano.gov/.

Despite the current interest nanoparticles are not a new phenomenon, with scientists being aware of colloids and sols, for more than 100 years. The scientific investigation of colloids and their properties was reported by Faraday (1857) in his experiments with gold. He used the term "divided metals" to describe the material which he produced. Zsigmondy (1905) describes the formation of a red gold sol which is now understood to comprise particles in the

10 nm size range. Throughout the last century the field of colloid science has developed enormously and has been used to produce many materials including metals, oxides, organics and pharmaceutical products.

Many other well known industrial processes produce materials which have dimensions in the nanometre size range. One example is the synthesis of carbon black by flame pyrolysis which produces a powdered form of carbon with a very high surface to mass ratio. This is usually highly agglomerated but has a primary particle size which can be of the order of 100 nm. Worldwide production of carbon black was approximately 6 million tonnes in 1993 (IARC, 1996). Other common materials produced by flame pyrolysis or similar thermal processes include fumed silica (silicon dioxide), ultrafine titanium dioxide (T_iO_2) and ultrafine metals such as nickel.

Other industrial processes create and use nanoparticles as part of the process. An example of this is thermal spraying and coating. In this process, a coating material (usually metal) is vaporised in a gas flame or plasma and deposited as a thin film onto a surface to improve its hardness or corrosion resistance. Elsewhere nanoparticles are an undesirable by-product of an industrial process. The most obvious example of this is welding which can generate large quantities of nanoparticles usually in the form of a well defined plume of aggregated nanoparticles. Particles in the nanometre size range are also produced in large quantities from diesel engines and from domestic activities such as gas cooking.

Nanometre sized particles are also found in the atmosphere where they originate from combustion sources (traffic, forest fires), volcanic activity, and from atmospheric gas to particle conversion processes such as photochemically driven nucleation. In fact, nanoparticles are the end product of a wide variety of physical, chemical and biological processes, some of which are novel and radically different, others of which are quite commonplace.

It is widely acknowledged that there is a lack of information concerning the human health and environmental implications of manufactured nanomaterials and concerns have been expressed regarding potential risks to health which might arise during their manufacture, use and disposal (e.g. DG SANCO 2004). This report also stated that the “biological activity of nanoparticles – including potential adverse as well as beneficial effects - tends to increase as their size decreases”. Evidence for other particle types (e.g. “low toxicity dusts”) clearly shows that the toxicity of these materials is strongly dependant on their surface area (Tran *et al*; 2000). Such ideas are consistent with current views on the links between environmental pollution and health. Epidemiological evidence from industrial processes, such as the manufacture of carbon black, where in principle workers may potentially be exposed to nanoparticles, also indicates potential (respiratory) health issues (Gardiner *et al;* 1992). The large surface area, crystalline structure, reactivity and exotic properties of some nanoparticles, coupled with what appears to be an imminent shift away from laboratory based development to industrial manufacture, strongly indicates a need for a clearer understanding of the risks associated with these materials.

Because of these issues, the Royal Academy of Engineering and the Royal Society have recently established a working group to consider the potential health risks arising from the development of nanoparticles and nanotechnology in general (http://www.nanotec.org.uk). It is expected that this working group will report later in the year.

In anticipation of this report, the Health and Safety Executive (HSE) has commissioned a review of the occupational hygiene implications of the deliberate manufacture of nanoparticles to help formulate their strategy and response. This report describes the outcome of the work.

2. SCOPE AND AIMS

Nanoparticles are the end product of a wide variety of physical, chemical and biological processes, some of which are novel and radically different, others of which are quite commonplace. In this review, based on the resources available and on discussions with the sponsors, we have focussed on processes for the deliberate development and manufacture of nanoparticle products. Hence we have specifically not considered the extensive literature on combustion or environmental sources of nanoparticles, which are primarily environmental pollution issues. These have been reviewed in detail in relation to the setting of environmental standards.

For nanoparticle manufacturing processes we have considered:

- potential routes for human exposure;
- industrial sources of occupational exposure;
- level of exposure;
- means of, and effectiveness of control measures;
- potential numbers exposed;
- ease with which gaps in knowledge could be filled;
- trends in the (potential) use of nanotechnology;
- views as to the likely impact, including timescales, of the implementation of the change from research use to full-scale industrial use.

Where possible we have discriminated between processes which are new (new processes), and existing processes. New processes include those which are adapted to produce new forms of nanoparticle, or to produce them in a novel way, or processes which are likely to be scaled up to manufacture significant (bulk) quantities of product. We consider that it is from these new processes that as yet unrecognised risks are more likely to emerge.

Our focus has been on the production processes rather than on those which utilise nanoparticles to manufacture other products. Our view of a production process includes synthesis, in which the material is formed, and recovery in which the product is collected, modified or adapted, divided and packed for dispatch. It does not include processes in which nanoparticle materials are imported into a site and used as a feedstock or component. At this stage this is logical given our emphasis on new processes and new materials. Since these are new materials, most of the research and industry effort is on the development of processes and materials and of the scale-up of these processes to industry scale. Hence most of those who may be exposed are currently working in this part of the industry. As understanding about the properties of a new material increase, effort will tend to shift towards applications and uses and more exposures might be expected there. Secondly, in the early stages of the life cycle of a new material, many of the potential applications will be speculative and may never come to fruition. Effort spent in investigating potential scenarios, yet to be developed would not be useful at this stage (although these scenarios must be considered as they emerge).

Finally, in this review, we have not reviewed the toxicity of nanoparticles. A separate toxicological review is currently being undertaken in parallel by the HSE and is expected to report in June 2004 (Fraser *et al;* 2004).

3. METHODS

In carrying out this review, it was anticipated that while there would be relevant studies in the scientific literature dealing with existing processes (e.g. carbon black), few studies would be identified in which occupational exposure to nanoparticles in new processes had been investigated. A standard review of the peer-reviewed literature was therefore considered insufficient and so the review comprised four main elements:

- A "conventional" literature review of the literature focussing primarily on powder-handling industries (TiO_2, ultrafine carbon black) to identify scenarios, exposures, numbers of workers exposed in the UK and relevance to "new technology" nanoparticle processes.

- A web based review to identify key information on the nature of nanoparticles, manufacturing processes, current and future applications, numbers of people involved, key researchers and organisations operating in the field.

- Discussions with key researchers and organisations involved in the manufacture of nanoparticles.

- Integration and interpretation of all of this information plus other information and insights of the IOM project team into a coherent review report.

3.1 CONVENTIONAL LITRATURE AND WEB BASED REVIEW

Standard literature search techniques were used to identify applicable scientific literature.

The online databases used included:

- NIOSHTIC/NIOSHTIC 2 – This is a bibliographic database with comprehensive international coverage of documents on occupational health and safety. It contains detailed summaries of over 200,000 articles, reports and publications, spanning over 100 years.

- OSHLINE – This complements NIOSHTIC with comprehensive coverage of journals and reports on occupational health and safety.

- CISILO – This is a bilingual bibliographic database with references to international occupational health and safety literature.

- HSELINE – This database contains more than 184,000 abstracts for worldwide literature on occupational health and safety. This is predominantly oriented towards safety and industrial hazards with an emphasis on areas including engineering, manufacturing, agriculture hazardous substances and occupational hygiene.

- CANADIANA – This provides references to occupational health and safety documents published in Canada, about Canadian subjects, or by Canadian authors. It includes references on reports, articles, conference proceedings, monographs and unpublished materials, or limited distribution material.

These databases are available from the Canadian Centre for Occupational Health and Safety References Collection, URL:http://ccinfoweb.ccohs.ca/bibliographic/search.html.

- The Barbour Index – This database contains full text documents from various government organisations, professional bodies, research institutions and trade associations and is available at http://www.barbour-index.co.uk/content/home/.

- Science Direct - This is available at http://www.sciencedirect.com and features a range of academic databases. Subjects covered include environmental science, microbiology, medicine and social sciences.

The initial searches included a wide range of search terms, singly or in combination as necessary and these are detailed in Appendix 1. The relevance of the identified information sources was assessed firstly on the basis of the article's title and secondly on the contents of the abstract. The full text was then obtained for those articles deemed suitable for inclusion. Where possible, key review or summary articles were reviewed in the first instance, being supplemented with other publications as need be.

Web based searches were also carried out using general on-line search engines such as GOOGLE (http://www.google.com), ALTA-VISTA (http://www.altavista.com) and YAHOO (http://www.yahoo.com). Key web sites more specific to nanotechnology and the review in general were also identified and searched. These included:

- National Nanotechnology Initiative: http://www.nano.gov
- The Institute of Nanotechnology (ION): http://nano.org.uk
- Nanotechnology and Nanoscience: http://www.nanotec.org.uk/
- Community Research and Development Information Service - nanotechnology http://www.cordis.lu/nanotechnology/
- The Foresight Institute: http://www.foresight.org
- INEX: Nanotechnology Exploitation web site: http://www.inex.org.uk
- The NanoInvestors News: http://www.nanoinvestornews.com/
- National Statistics Online: http://www.statistics.gov.uk/
- Various UK University and Research departmental web sites.

3.2 STRUCTURED INTERVIEWS

Structured telephone interviews were undertaken with key individuals to obtain further information about the current nanoparticle industry, its future developments and associated regulatory aspects. Participants were selected because of their prominence in relation to scientific or industrial development of nanoparticles or their health effects or risk assessment.

4. PHYSICAL CHARACTERISTICS/PROPERTIES OF NANOPARTICLES

4.1 TERMINOLOGY AND DEFINITIONS

In occupational hygiene; the importance of particle size in relation to the transport of aerosols in a workplace, the probability that the aerosol will be inhaled, the region of the respiratory tract that it will reach and whether or not it will deposit has been well understood for some time. This has led to established criteria for the measurement of occupational exposure to airborne particles, based on measures of particle size. These criteria, for the inhalable, thoracic and respirable fractions, have been agreed by ISO (International Standards Organisation) and ACGIH (American Conference of Governmental Industrial Hygienists) and CEN (European Committee for Standardisation) (CEN, 1993; ACGIH, 1993; ISO, 1993).

The CEN document, EN 481 “Workplace Atmospheres – size fraction definitions for measurement of airborne particles” (CEN 1993) provides satisfactory definitions of the inhalable, thoracic and respirable size fractions, and target specifications (conventions) for sampling instruments to measure these fractions. The standard defines sampling conventions for particle size fractions which are to be used in assessing the possible health effects resulting from inhalation of airborne particles in the workplace. In principle they are derived from experimental inhalation data for healthy adults. Conventions are defined for the inhalable, thoracic and respirable fractions; extra-thoracic and tracheo-bronchial conventions may be calculated from the defined conventions. Conventions are stated in terms of mass fractions, but they may also be used when the intention is to evaluate the total surface area or the number of particles in the collected material.

The size fractions are expressed in terms of aerodynamic diameter of a particle which is a measure of its behaviour in air. Aerodynamic diameter is a form of “equivalent diameter” often used in aerosol measurement. The aerodynamic diameter of a particle is defined as the diameter of a sphere of density 1g cm^{-3} with the same terminal velocity (falling speed) due to gravitational force in calm air as the particle under the prevailing conditions of temperature, pressure and relative humidity (CEN, 1993). For particles of aerodynamic diameter less than 0.5 μm, the particle diffusion diameter should be used instead of the particle aerodynamic diameter. For diffusion, the appropriate “equivalent diameter” is the diffusion diameter. This is defined as the diameter of a sphere with the same diffusion coefficient as the particle under the prevailing conditions of temperature, pressure and relative humidity.

The CEN standard defines the inhalable fraction as the “mass fraction of total airborne particulates which is inhaled through the nose and mouth”. In CEN (1993) the inhalable convention is defined as the percentage E_I of airborne particles of aerodynamic diameter D in micrometers which are to be collected where E_I is given as;

$$E_I = 50(1 + \exp[-0.06D]) \qquad (1)$$

The thoracic fraction is defined as the mass fraction of inhaled particles penetrating beyond the larynx (CEN, 1993). The thoracic convention may be described either as a fraction of the total suspended particulate or as a sub-fraction of the inhalable fraction. The convention is defined as:

“The thoracic fraction defined as a fraction of the inhalable fraction (E_T) shall be given as a cumulative log-normal distribution with a mass median aerodynamic diameter of 11.64 microns and a geometric standard deviation of 1.5. (This is equivalent to a median of 10

microns when the convention is expressed as a fraction of the total aerosol. The thoracic fraction, expressed as a fraction of total aerosol, is given by E_T *.*E_I*.") (CEN, 1993).*

The respirable fraction is defined as the mass fraction of inhaled aerosol penetrating to the un-ciliated airways of the lung. Like the thoracic convention, the respirable convention is described either in terms of total or inhalable aerosol.

"The respirable fraction, defined as a fraction of inhalable (E_R*) is described by a cumulative log-normal distribution with a mass median aerodynamic diameter of 4.25 microns and a standard deviation of 1.5. (This is equivalent to a median of 4.0 microns when the convention is expressed as a fraction of the total aerosol. The respirable fraction, expressed as a fraction of total aerosol, is given by* E_R *.*E_I*.)" (CEN, 1993).*

Although in common use, the terms ultrafine particle, ultrafine aerosol, nanoparticle and nanoparticle aerosols, have not been so rigorously defined.

A simple search of Science Direct (www.sciencedirect.com) identified 1321 papers in which the term "ultrafine particles" had been used. In many of these the term was used without definition. Where definitions were provided, most often in relation to the measurement of environmental aerosols, there was broad agreement that ultrafine particles were those with a diameter "less than" 100 nm (e.g. Preining, 1998). Generally this was taken to imply the physical diameter of the particles although it could imply a diffusion diameter as instruments to measure particles in this size range often use diffusion as a classifying mechanism. This is discussed in more detail in Section 4.4. Particles are seldom present as a single size (monodisperse) but rather can be represented by a distribution of sizes which is commonly characterised by median (in terms of mass or number) and a geometric standard deviation. This simplistic definition (less than 100 nm) fails to take account of size distribution. It is not clear for example, whether the definition implies all particles less than 100 nm, 95% of particles less than 100 nm, a mean (or median) of less than 100 nm or any particles less than 100 nm. Sometimes, the term "nominal diameter" has been used to provide an effective dimension, where information about particle shape was not available or the particles were known not to be spherical. Similarly an ultrafine aerosol is an aerosol consisting of predominantly ultrafine particles Although this is reasonably consistent and certainly consistent with a recently proposed definition in an ISO working group (ISO, 2004) and the EPA (EPA, 2003), there is a lack of rigour in this definition which is not helpful.

The terminology used by industry can be much less consistent. For example, a website of a company involved in powder handling and processing defines micronising as the "production of an ultrafine powder with a top size of 20 microns", equivalent to 20000 nm (www.csminchem.co.uk). Also, the TSI P-Trak Model 8525 Ultrafine particle counter, counts particles in the size range 20 nm to greater than 1000 nm.

Few formal definitions of nanoparticles or nanoparticle aerosols have been published. The definition most often implied is from the definition of nanotechnology. For example, the Interagency Subcommittee on Nanoscale Science, Engineering and Technology (NSET) of the US Federal Office of Science and Technology Policy defines nanotechnology as: "Research and technology development at the atomic, molecular or macromolecular levels, in the length scale of approximately 1 - 100 nanometre range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size. The novel and differentiating properties and functions are developed at a critical length scale of matter typically under 100 nm". (EPA, 2003). A similar definition has been proposed by the Royal Society, "Nanotechnology is the production and application of structures, devices and systems by controlling shape and size at nanometre scale." (Royal

Society, 2004). Although not specifically describing nanoparticles, these definitions imply a nanoparticle definition of particle less than 100 nm.

Whether this simple definition is satisfactory is doubtful. It does not take account of the issue of the size distribution nor does it take account of particle behaviour or properties. It is probable that particles with a dimension of 100 nm will have different properties from those with a dimension of 5nm or 1nm. Particles smaller than 5nm will contain only a few molecules, with a high proportion of these at the surface. The structure of such particles cannot be regarded as a continuum and traditional concepts of particle volume and surface area are no longer prime parameters (Preining, 1998).

There is some recognition of this in ISO (2004), which contains a proposal that a nanoparticle is defined as “A particle with sufficiently small diameter for physical and chemical properties to differ measurably from those of the bulk material. A nominal but not exclusive upper diameter for nanoparticles is 40nm.”

A further key issue to consider is the role of agglomerates. It is useful here to distinguish between aggregates and agglomerates. These terms are not used rigorously in the literature but in ISO (2004) the following definitions are proposed;

- Agglomerate: A group of particle held together by relatively weak forces, including Van der Waals forces, electrostatic forces and surface tension.
- Aggregate: A heterogeneous particle in which the various components are not easily broken apart.

Hence while an aggregate many be considered to be permanent, agglomerates may break up under certain circumstances. The issue is therefore whether an aerosol of primary particles in the nanometre scale which exist as loosely bound agglomerates in the micrometer scale can be considered a nanoparticle aerosol? This has important implications for how these aerosols are measured or even detected. The rationale for including these agglomerated aerosols as nanoparticle aerosols is that in the lung (or other target organ), these may break up resulting in primary nanometre scale particles becoming distributed in the respiratory tract. Oberdorster *et al* (1994) found that particles in the form of aggregated TiO_2 aerosol had increased toxicity when compared with an aerosol of larger TiO_2 particles, even though both aerosols were similar in aerodynamic size distribution. This issue is discussed in more detail in Section 4.2 and in the companion toxicological review which is being carried out (Fraser *et al;* 2004).

It is understood that the German MAK (Maximale Arbeitsplatzkonzentration Kommision) is considering the issue of agglomeration and are moving towards an ultrafine particle definition of the form: “Ultrafine Particles (Nanoparticles) including their agglomerates and aggregates as components of dusts or fumes. Their primary particles are characterized by a diffusion-equivalent-diameter of less than 100nm.” (Darman, 2004). The logic of a definition of this type would also hold for a definition of nanoparticles.

As yet there is no satisfactory agreed definition of a nanoparticle or nanoparticle aerosol.

4.2 NANOPARTICLE CLASSIFICATION

4.2.1 Introduction

The development of new nanomaterials is a rapidly progressing science and it is beyond the scope of this review to track all of these developments. However several excellent summaries are available. A recent special edition of the Journal of Materials Chemistry (Rao, 2004) published 47 papers concerning the development of new nanomaterials including metallic nanoparticles, germanium, ceramic and aluminium oxide nanowires, carbon, silicon and germanium nanotubes, zinc oxide nanocrystals, gold nanowafers and copper oxide nanocubes. A comprehensive overview of the whole science of nanomaterials, including theory, synthesis, properties and applications has recently been published by Rao *et al* (2004).

Nanoparticles can be formed by a variety of methods with different methods also being used to form the same type of nanoparticles. For example, metal nanoparticles can be synthesised by various processes including laser ablation, condensation from vapour, thermal decomposition, and wet chemical reduction of the corresponding metal salts (Johans, 2003). The various synthesis processes are discussed in more detail in Section 5.

Particle morphology is a useful basis for categorising nanoparticles. Table 4.1, adapted from Jorter and Rao (2002), summarises the main categories of nanoparticle according to their morphologies, material from which they may be composed and the type of application in which they may be used.

Table 4.1: Nanoparticles – categories and applications

Nanostructure	Example Material or Application
Nanotubes	carbon, (fullerenes)
Nanowires	metals, semiconductors, oxides, sulfides, nitrides
Nanocrystals, quantum dots	insulators, semiconductors, metals, magnetic materials
Other nanoparticles	ceramic oxides, metals

4.2.2 Nanotubes

Nanotubes are a particularly novel form of nanoparticle about which there is great interest and excitement. Carbon nanotubes (CNT) were first discovered by Iijima (1991), and are a new form of carbon molecule. They are similar in structure to the spherical molecule C60 (buckminsterfullerene or bucky balls) discovered in the 1980s (Kroto *et al*; 1985) but are elongated to form tubular structures 1-2 nm in diameter. They can be produced with very large aspect ratios and can be more than 1 mm in length. In their simplest form, nanotubes comprise a single layer of carbon atoms (single molecule) arranged in a cylinder. These are known as single-wall carbon nanotubes (SWCNTs). They can also be formed as multiple concentric tubes (multi-wall carbon nanotubes, MWNTs) having diameters significantly greater, up to 20 nm, and length greater than 1 mm.

CNTs have great tensile strength and are considered to be 100 times stronger than steel whilst being only one sixth of its weight thus making them potentially the strongest, smallest fibre known (www.thomas.swan.co.uk). They also exhibit high conductivity, high surface area, unique electronic properties, and potentially high molecular adsorption capacity (Maynard *et al;* 2004). Applications which are currently being investigated include; polymer composites (conductive and structural filler), electromagnetic shielding, electron field emitters (flat panel displays), super capacitors, batteries, hydrogen storage and structural composites.

Hofman *et al* (2003) identified four main synthesis methods for CNTs. These are:

- laser ablation (Ebbesen and Ajayan, 1992),
- arc discharge (Ebbesen and Ajayan, 1992),
- chemical vapour deposition (CVD) (Colomer *et al*, 2000) and;
- plasma-enhanced CVD.

Many of the applications envisaged for CNTs will require bulk quantities of the material to be produced. For applications where large quantities of CNTs are required, CVD offers the most suitable approach for scaling up due to the relatively low growth temperature, high yields and high purities that can be achieved (Singh *et al;* 2003). Production of relatively large volumes of unaligned MWCNTs, have been achieved by this and other methods and these materials are beginning to be used for commercial applications.

A recent advance in the development of CNTs is the production of controlled (in terms of pattern and length) architectures of aligned CNTs (Singh *et al;* 2003) using an injection CVD process. The CNTs are produced by spraying a solution of ferrocene dissolved in xylene into a two-stage furnace. The carrier gas is a mixture of argon and hydrogen. The ferrocene decomposes to provide an iron catalyst, which nucleates the nanotube growth. The xylene acts as the carbon feedstock. The vapour passes into the second furnace where the nanotubes grow on quartz substrates.

One major focus of current research on nanotubes is on scaling-up of production rates to kilogram quantities. Commercial manufacturing and supply of CNTs at these levels has recently begun in the UK by the company Thomas Swan (www.thomas-swan.co.uk). Nanotubes have also been produced from other materials including silicon and germanium but the development of various forms and applications for CNTs remains the main focus of activity. More information about nanotubes can be found on the many websites dedicated to their production and application. A good starting link to these is the Nanotube Site (www.pa.msu.edu/cmp/ntsite/nanopage).

From an occupational hygiene perspective, the large aspect ratios of CNTs, their durability and the desire to produce bulk quantities make them of particular interest.

4.2.3 Nanowires

Nanowires are small conducting or semi-conducting nanoparticles with a single crystal structure and a typical diameter of a few 10s of nanometres and a large aspect ratio. They are used as interconnectors for the transport of electrons in nanoelectronic devices. Various metals have been used to fabricate nanowires including cobalt, gold and copper. Silicon nanowires have also been produced.

Most approaches to the fabrication of nanowires are derived from methods currently used in the semi-conductor industry for the fabrication of microchips. Van Zant (2000) provides a comprehensive review of microchip fabrication which makes useful background reading. Typically they involve the manufacture of a template followed by the deposition of a vapour to fill the template and grow the nanowire. Deposition processes include Electrochemical Deposition and CVD. The template may be formed by various processes including etching, or the use of other nanoparticles, in particular, nanotubes.

4.2.4 Quantum dots

Quantum dots of semiconductors, metals and metal oxides have been at the forefront of research for the last five years due to their novel electronic, optical, magnetic and catalytic properties (www.oxonica.com). The number of atoms in a quantum dot, which range from 1000 to 100,000, makes it neither an extended solid structure nor a single molecular entity. This has led to various names being attributed to such materials including nanocrystals and artificial atoms. To date, chemistry, physics and material science have provided methods for the production of quantum dots and allow tighter control of factors affecting, for example, particle growth and size, solubility and emission properties.

The majority of research has centred around semiconductor quantum dots, as they exhibit distinct 'quantum size effects'. The light emitted can be tuned to the desired wavelength by altering the particle size through careful control of the growth steps. Various methods can be employed to make quantum dots however the most common is by wet chemical colloidal processes.

4.2.5 Other nanoparticles

This catch all category includes a wide range of primarily spherical or aggregated dendritic forms of nanoparticles. Dendritic forms are where spherical or other compact forms of primary particles aggregate together to form chain like or branching structures. Welding fume is the best known example of this. This “other nanoparticle” category includes existing common nanoparticles such as ultrafine carbon black and fumed silica which are synthesised in bulk form through flame pyrolysis methods. Nanoparticles of this type may be formed from many materials including metals, oxides, ceramics, semiconductors and organic materials. The particles may be composites having, for example, a metal core with an oxide shell or alloys in which mixtures of metals are present. Examples of these types of materials may be found on the QinetiQ website
http://www.nano.qinetiq.com/02_products_materials/default.asp.

Many of the production processes involve the direct generation of aerosols through gas phase synthesis, similar to flame pyrolysis but other production processes including wet chemistry methods and attrition methods may be used. This group of particles may be categorised as being less well defined in terms of size and shape, generally larger (although still within what could be considered nanoparticles), and likely to be produced in larger bulk quantities than other forms of nanoparticles. From an occupational hygiene perspective, the likelihood of aerosol generation and their availability in bulk quantities makes these nanoparticles of particular interest.

4.3 EXPOSURE METRICS

4.3.1 Inhalation

Exposure to fine particulate dusts is known to lead to pulmonary diseases. The idea that any poorly soluble particles administered in sufficient quantities to the lung can cause an inflammatory reaction has arisen following the demonstration of rat lung overload (Mauderly *et al;* 1994). An important challenge in particle toxicology is to define the quantity that produces inflammation i.e. define the effective dose. Since the late 1980’s, toxicological evidence has been emerging indicating that the health effects associated with inhaling ultrafine particles may not be closely associated with particle mass. Early studies with PTFE **(**polytetrafluoroethylene) particles around 20 nm in diameter showed that airborne concentrations of a supposedly inert insoluble material lower than 50µg m-^{3} could be fatal to rats (Johnston *et al*; 2000). Since then, many studies have indicated that the toxicity of insoluble materials increases with decreasing particle size, on a mass for mass basis (Faux *et al;* 2003).

Traditionally the dose of particle administered to the lung, e.g. in an instillation or inhalation situation, is measured in mass. A number of recent studies indicate that the inflammatory response depends on the surface area of particles deposited in the proximal alveolar region of the lungs (Tran *et al*; 2000; Faux *et al;* 2003). Thus, particle surface area is a better metric than mass for relating the particle dose to the inflammatory reaction. The precise mechanisms by which these materials exhibit higher levels of toxicity, at smaller particle sizes, have yet to be elucidated, although it is now understood that oxidative stress plays an important role in initiating the chain of events, at the molecular and cellular level, leading to the observed health effects. This was demonstrated in a recent study in which *in vitro* experiments with a range of poorly soluble particles were conducted (Faux *et al;* 2003). The data generated by this study were able to demonstrate a relationship between the surface area dose and inflammatory response *in vitro* and the earlier *in vivo* results. This discovery has important practical and theoretical implications. At the theoretical level, it has highlighted the role of the epithelial cells in the proximal alveolar region, their interaction with the deposited particles and the ensuing molecular events leading to inflammation. At the practical level, it has offered a new approach to interpreting *in vitro* data, a cost effective way of screening new materials for toxicity and an alternative way to animal testing. But particles also exist in a wide range of surface reactivity. Upon deposition in the pulmonary region, such reactivity exerts an oxidative stress on the cells *via* contact between particle/cell surface area. Consequently, both highly reactive particles with a low surface area and low toxicity particles with a high surface area can exert the same oxidative stress level on the cells they come into contact with. When this inhaled dose reaches a critical level, an inflammatory response occurs. For low toxicity dusts, inflammation will diminish with the cessation of exposure, while for high toxicity dusts, inflammation will persist (Tran *et al;* 2000). Persistent inflammation is likely to lead to diseases such as fibrosis and cancer. Thus it is important to control inflammation. This can be done if we can (i) determine the critical dose of particles that initiates inflammation and (ii) set exposure limits, according to the relevant metric, so that such a dose cannot be reached within a lifetime exposure scenario.

Regulations for the control of airborne particle pollution in the workplaces are currently mass based and vary between particulate types (HSE, 2002b). A proper description of the metric of the particle dose would provide a coherent and consistent body of knowledge on particle toxicity and would, in turn, facilitate a coherent and rational policy for regulating dust exposure in the workplace.

Thus, it is apparent that measuring exposures against mass alone is not sufficient. Of the three primary exposure metrics (mass, surface area, and number), there is compelling evidence to suggest that occupational nanoparticle aerosols should be monitored in terms of surface area. The concentration of nanoparticles might be very small in terms of mass, quite large in terms of surface area and huge in terms of particle number. However, the estimate of surface area does depend on the measurement technique used. Depending on how much detail of the surface is inspected, the measurement can increase significantly. For example, if a prune is seen as approximately a sphere then it has approximately the surface of a smooth sphere of the same diameter; but if the surface of the wrinkles is included then its surface area becomes notably larger. Similarly, with techniques that use adsorption of gas molecules on to the surface of the particle to measure the surface, the smaller the gas molecule chosen, the more it can enter the wrinkles on the particle surface. Nitrogen as the gas molecule for adsorption and measurement of surface area may be a good choice, but other gases (or other surface measurement techniques) are worth considering. Biologically relevant surface area is likely to be that accessible to biologically relevant molecules in the body.

So far, we have assessed the risk of pulmonary disease from inhaled particles. However, it has also been suggested that due to their small diameter, nanoparticles are capable of penetrating epithelial cells, entering the bloodstream from the lungs (Gilmour *et al;* 2004), and even translocating to the brain via the olfactory nerves (Oberdorster *et al;* 2004). The ability of inhaled nanoparticles to disperse beyond the lungs suggests that the health effects of nanoparticles may not be confined to the lungs. Also, nanoparticles cleared by macrophages via the mucociliary escalator, can be swallowed and therefore available for transfer to other body organs via the gastro-intestinal compartment. There is also some evidence that smaller particles can be transferred more readily than their larger counterparts across the intestinal wall (Behrens *et al;* 2002). Little is currently known about the health effects of nanoparticles on the liver and kidneys as well as the correct metric for describing the nanoparticle dose in these organs. Another area which merits further research is the transfer of nanoparticles across the placenta barrier. Exposure to nanoparticles during the critical window of foetal development may lead to developmental damage in the offspring.

While a strong case may be made for using aerosol surface area as a dose metric, this may not be universally so. For example, for fibrous aerosols such as asbestos and glass fibre, the currently accepted best approach is to count fibres (i.e. the metric is particle number). Some types of nanoparticle could be considered fibres. Carbon nanotubes for example have high aspect ratios and are durable. They can be manufactured with lengths well within the range conventionally considered to be a fibre (although their diameters are much smaller than we could detect with current standard counting methods which are based on optical microscopy). Until we know more about the toxicological responses to these materials it is not possible to give a definitive answer to this issue.

In any case, it is also necessary to consider characterising exposures against aerosol mass and number concentration until further information and improved methods are available (Section 4.4). For each of these exposure metrics, but particularly in the case of mass concentration, size-selective sampling will need to be employed to ensure only particles within the relevant size range are sampled.

4.3.2 Dermal exposure

The importance of dermal exposure to hazardous substances continues to increase. The U.K. HSE estimate that there are around 85,000 cases of work related skin disease at any one time, with people employed as bricklayers, laboratory technicians and hairdressers being at particular risk (Hodgson *et al;* 1993). Substances which are considered to be potentially harmful include pesticides such as methyl parathion and solvents such as carbon tetrachloride. Harmful effects arising from skin exposure may either occur locally within the skin or alternatively the substance may be absorbed through the skin and disseminated via the bloodstream, possibly causing systemic effects.

Because of this there have been considerable efforts made to develop quantitative methods for monitoring skin exposure. All of these techniques essentially measure the mass of material deposited onto the skin, either per body part or per unit area of skin exposed. Difficulties in this area are compounded by a multitude of measuring methods which are not easily comparable. The development of a conceptual model of dermal exposure has been beneficial in clarifying some of these issues (Schneider *et al;* 2000).

Systemic effects in particular are unlikely to depend only on the mass on the skin but are more likely to be related to uptake through the skin. Uptake is the flux through the skin and will depend on the concentration through the skin, the area exposed and the duration of exposure. Because of this some authors have suggested that uptake is a more appropriate metric than mass (Robertson and Cherrie, 1995).

A recent review of dermal exposure issues concluded that there was no evidence to indicate that specific health problems are currently arising from dermal penetration of ultrafine particles (HSE, 2000). However, the review conceded that dermal absorption of ultrafine particles (nanoparticles) has not been well investigated and suggested that ultrafine particles may penetrate into hair follicles where constituents of the particles could dissolve in the aqueous conditions and enter the skin. Direct penetration of the skin has been reported by Tinkle *et al* (2003) for particles with a diameter of 1000 nm, much larger than nanoparticles. It is reasonable to postulate that nanoparticles are more likely to penetrate, but this has not yet been demonstrated. Several pharmaceutical companies are believed to be working on dermal penetration of nanoparticles as a drug delivery route.

Any metric proposed to assess dermal exposure to nanoparticles should be biologically relevant and should relate to health effects. Further work including workplace studies and *in-vitro* assessment of penetration is required. Based on the current level of knowledge, measurement approaches should include assessment of mass, particle number, concentration, area exposed and duration of exposure.

4.3.3 Ingestion exposure

In occupational settings very little work has been done up to now on ingestion exposure. Lead is one of the few materials where the ingestion route has received some attention. Lead paint removal activity can produce high ingestion exposures via hand-mouth contact and food contamination in certain workplaces. A recent study has shown that workers involved in the supply and removal of scaffolding can have particularly high blood lead levels as a result of hand contamination and subsequent ingestion (Sen *et al*; 2002). No work was identified in relation to ingestion exposure of nanoparticles. Metrics to assess ingestion exposure to nanoparticles should be biologically relevant and (probably) in the first instance should be measures of mass uptake.

In conclusion, scientific evidence, so far, has demonstrated that particle surface area and surface reactivity is likely to be the metric of choice to describe the inflammatory reaction to deposited particles in the proximal alveolar region of the lung. For nanoparticles, their potential dispersal to other organs as well as the possibility of exposure by other routes such as dermal or ingestion mean that possible health risks beyond the lung can not be ruled out. Further research to generate vital data on the possible mode action of nanoparticles in the extra-pulmonary system is needed in order to assess realistically the health risks to nanoparticle exposure.

4.4 MEASUREMENT OF NANOPARTICLES

Current best practice to measure the exposure of an individual to a chemical or other material present as an aerosol is to use a personal sampling device to collect a sample of the aerosols most appropriate, biologically relevant fraction (HSE, 2000). In occupational hygiene, it is common practice to use samplers conforming to the inhalable or respirable convention. Samples collected in this way, usually over a full working shift, are then subsequently assessed either gravimetrically or via chemical analysis to determine the mass, and hence average concentration over the defined period. These samplers provide an estimate of time weighted mass concentration, from which personal exposure may be derived.

It is clear from the discussion of exposure metrics in Section 4.3 that for nanometre size aerosols, measurement of mass is not sufficient. Particle number would be a more appropriate metric than mass, though ideally the preferred metric would be particle surface area. Hence an ideal sampler to measure biologically relevant exposure to nanoparticle aerosols would be a personal sampling device which collects a relevant size fraction and provides either an instantaneous measure of the sample surface area or which facilitates the off-line analysis of the sample to provide a measure of surface area. Unfortunately there are no systems which currently provide a solution of this type.

Table 4.2 provides a summary of the various types of devices which might be or have been used to provide measurement information on nanometre size aerosols.

Table 4.2 Summary of methods for the analysis of nanoparticles

Metric measured	Method	Comment
Mass	Size selective personal sampler	No current devices with a size fraction cut-off in the nm size range but could be developed Static device would overcome limit of detection issues
Number	Optical Particle Counter	Particles smaller than 300 nm not detected
	Condensation particle counter (CPC)	Real time number concentration, up to 100 nm
	Scanning mobility particle sizer (SMPS)	Real-time Real-time size selective, based on mobility diameter 3 – 800 nm
	Electrical low pressure impactor (ELPI)	Real time size selective (aerodynamic diameter) detection of number concentration. Sample collection
Surface area	Epiphaniometer	Radioactive tagging based on (Fuchs) surface area
	BET bulk analysis	Estimates based on gas adsorption
Image analysis	SEM/TEM	Analysis of morphology Samples may be collected by personal samplers or size selective static samplers

Assessment of mass could be based on a size selective personal sampler with a cut-off point of approximately 100 nm (or at some other point in the nanometre size range). The sample could be analysed by weighing or by chemical analysis. There are no commercial devices of this type currently available, but there is no reason in principle why they could not be developed in the future. Particle size selective stages based on diffusion would make appropriate pre-selectors for devices of this type. However, at flow rates typical for current personal samplers (up to five litres per minute) one limitation could be the mass which would be collected. Given a typical limit of detection for a gravimetric sample collected on a filter of 0.01mg, the lowest measurable concentration based on a full shift collection would be 0.02 mgm^{-3}.

An important issue here relates to what amount of nanoparticle material would be necessary to measure by this or any other method. To be useful, a measurement method needs to have a limit of detection which is lower than that at which it is considered that health effects might occur based on either toxicological or epidemiological studies. For all new nanoparticles and for many existing nanoparticles, a health effects level has not been established (Fraser *et al;* 2004). Health effect levels for any nanoparticle are likely to be highly dependent on the specific particle, its morphology, surface, composition and size.

Provided that a satisfactory judgement about an effective level could be made, the limitation of detection issue could be overcome by using a high-volume static device with an appropriate cut point. No devices of this type are in common use nor have they been used to assess concentration levels associated with nanoparticle production.

Simple optical particle counters such as the Grimm 1.104 Work-Check (http://www.dustmonitor.com/monitors/occupational/1104.htm) or SKC 3886 Handheld Laser Particle Counter (www.skcinc.com) have a lower detection size-limit which is governed by the wavelength of their light source. In most cases this means that they cannot “see” or count particles less than 300 nm. As a result, these devices have little value in the measurement of nanoparticles.

There are however, several more sophisticated devices which can provide estimates of particle number concentration, some of which have been used in studies investigating nanoparticle exposure levels (e.g. Wake, 2001; Maynard *et al;* 2004). None of these are personal sampling devices.

The most widely used type of instrument for detecting and counting nanoparticle aerosols is the Condensation Particle Counter (CPC). These devices operate by condensing vapour onto sampled ultrafine particles to grow them to a size range that can be detected optically by a standard optical counter. A particularly useful example of this type of device is the TSI Model 3007 Condensation Particle Counter which is a hand held device, highly portable, with a claimed size range widow of 10 – 1,000 nm and a concentration range of 0-100,000 particles per cc (www.tsi.com). A limitation of this device is the lack of size information.

Instruments which provide both size and number information are not surprisingly, larger, more complex and more expensive. The most commonly used instrument of this type is the scanning mobility particle sizer (SMPS). Devices of this type (e.g. www.tsi.com) are capable of measuring aerosol size distribution from 3 to 800 nm, although not simultaneously over the complete range. The size distribution is expressed in terms of particle mobility diameter. The SMPS operates by charging particles and separating them based on their mobility passing between electrodes. Separated particles are then counted to give size range of mobilities. Application of these devices in occupational hygiene investigations has been limited due to their lack of mobility, expense and complications in use.

A more recent device is the Electronic Low Pressure Impactor (ELPI) sold in commercial form by Dekati (www.dekati.com). It is claimed that this device can measure particle size distribution and concentration in the size range 7 nm to 10 μm. In this device, sampled particles are charged and then passed into a low pressure impactor with electrically isolated collection stages. The electrical current carried by the charged particles onto each impactor stage is measured in real time by a sensitive multi-channel electrometer. The particle collection into each impactor stage is dependent on the aerodynamic size of the particles. After the collection period, collected particles can be removed from the impactor stages for further analysis. Other low pressure impactors such as the nanoMoudie (http://appliedphysicsusa.com/moudi.asp) are also available.

A major limitation of all of these measurement methods is that they cannot discriminate agglomerates of nanoparticles from single larger particles. As evidence does indicate that agglomerated nanoparticles can have increased toxicity compared to larger particles (Oberdorster *et al;* 1994), this limits the usefulness of these methods to assess exposure to aerosols of this type. (It is very probable that all nanoparticle aerosols will be agglomerated to some extent).

This issue of aggregation further indicates that measurement of surface area is preferable. The only instrument which has been successfully used to measure particle surface area directly is the Epiphaniometer (Gaggeler *et al*; 1989). In this device the aerosol is passed through a charging chamber where lead isotopes created from a decaying actinium source are attached to the particle surfaces. The particles are transported through a capillary to a collecting filter. The amount of radioactivity measured is proportional to the particle surface area. This is a complex and difficult instrument which has been used to measure the surface area of diesel particles but has not yet been used in occupational hygiene based studies of exposure. Details of these and other direct reading methods can be found in Kittelson (1998).

Measurements of surface area are more commonly carried out using bulk methods such as BET (Brauner-Emmett-Teller) analysis. This widely used process depends on gas adsorption using nitrogen, krypton, argon or carbon dioxide gases. The sample sizes used are typically greater than that which might be expected based on occupational hygiene sampling. Nevertheless this is an important measurement process by which bulk materials may be characterised and as such, could be used as part of an overall strategy for assessment of exposure.

In addition to these processes, there are a range of imaging processes which may be used along with scanning (SEM) or transmission electro-microscopes (TEM) to obtain size, shape, structure and in some cases compositional information from single or collections of aerosol particles. Conventional SEMs typically have a spatial resolution of 5-10 nm whereas TEMs can resolve down to about 1 nm. Samples can be collected directly onto filters, filter substrates or impaction substrates. Filters can collect particles smaller than their pore size, however it is preferable to use filters with a pore size comparable to the smallest particles of interest. Samples may also be collected directly on to SEM supports using electro-static precipitation or diffusion. Prior to imaging, samples are coated with gold and a commercial sputter coating device which deposits a layer of atoms a few nanometres thick under vacuum over the sample. Various commercial imaging packages are available to facilitate the analysis process.

Although it has higher definition, TEM often requires more complex arrangements for sample collection than the SEM. For both SEM and TEM there is an important need to calibrate the loading of the particles onto the sample filter correctly. It is necessary to provide sufficient coverage to allow analysis, but to ensure the particles do not touch or overlap. This can be particularly difficult in cases where samples comprise a wide range of particle sizes.

All of the measurement methods which may be used clearly fall short of what would be an ideal sampling and measurement system for nanoparticles. However, all have some potential to provide useful information about particular aspects of nanometre size particles, particularly when they are used in combination. The key issue is to develop an appropriate exposure assessment strategy, particular to the process and materials under consideration, which optimises the information available from the various sources. By using suitable combinations of instruments and methods, identification of appropriate surrogate measures and using appropriate models, taking account of determinants of exposure in a structured way and recognising the limitations of all of these, good information concerning the nature of the aerosol and in particular how it may change can be obtained. However, there is a pressing need for more research into the development of new and improved measurement methods, combination approaches and the development of generic strategies to provide reliable assessments of exposure to nanoparticles.

4.5 NANOPARTICLE BEHAVIOUR

Workers may be exposed to any material, during its production, use and disposal. As described previously, exposure to nanoparticles may in principle result from inhalation, ingestion or absorption through the skin. In general, occupational hygiene has largely focussed on exposure from the inhalable route based on the general belief that this was generally the highest in terms of risk. Hence an understanding of aerosol behaviour is necessary. Aerosol science is a well understood and described field of science which has been investigated and described over the last 100 years or so. Many excellent text books are available including Fuchs (1989), Davies (1966) and Friedlander (1977) which describe in great detail the fundamental properties of aerosols, their behaviour, their measurement and their applications.

Particle size is the principal parameter governing the behaviour of aerosols. Aerosol behaviour is governed primarily by inertial, gravitational and diffusional forces. For particles in the micrometre scale, inertial and gravitational forces dominate. As particle size decreases into the nanometre scale, diffusional forces dominate and particle behaviour is more like a gas or a vapour. In considering how nanoparticle aerosols may differ in behavioural terms from larger aerosols, important aspects include the rates at which particles diffuse, agglomerate, deposit and re-suspend. It is useful to consider the differences between large (inertial) and small (diffusional) particles in relation to aspects of exposure and control.

4.5.1 Diffusion

As particle size decreases towards the molecular level, their behaviour is more like that of a vapour (ICRP, 1994). The kinetic behaviour of nanoparticles follows basic laws of gaseous diffusion.

Particle diffusion (Brownian motion) occurs because particles suspended in a gas are bombarded by the molecules of the gas causing the particle to move in a random fashion. The rate at which particles diffuse is determined by the diffusion coefficient which is inversely proportional to the particle diameter. Particles with high diffusion coefficient have high mobility and mix rapidly in aerosol systems. Nanometre size particles will have much higher mobility than particles in the micrometer scale. This has implications for the ease in which they can be enclosed in systems or the ease in which they can be controlled.

In an enclosed system which has a leak, nanometre sized particles would be much more likely to escape than larger particles because of their higher mobility. Therefore for nanometre particle systems, an enclosure system design needs to provide a higher level of integrity than for micrometer sized aerosol systems. Systems normally used to contain gaseous emissions would be appropriate.

Where particles are released into the workplace atmosphere diffusion will cause migration from a higher concentration to a lower one. In this case nanometre size particles escaping will mix rapidly through the workplace air, and will be quickly dispersed. This has both positive and negative aspects. Nanoparticle aerosols will not remain localised so the concentration at the site of the leak will fall rapidly. However, leaking nanoparticles could end up at great distance from the source potentially leading to larger numbers of individuals being exposed.

4.5.2 Agglomeration

As a result of diffusion, particles will undergo multiple collisions leading to coagulation and agglomeration and growth in size. This is a principle mechanism in nanoparticle formation. The rate at which agglomeration occurs depends primarily on the number of particles (as concentration) and their mobility. Both of these increase as particle size decrease. Table 4.3 shows the agglomeration half-life of different concentrations of nanoparticles of various sizes.

Table 4.3 Coagulation half-life (from Preining, 1998)

Particle diameter	Half life			
nm	1 g m^{-3}	1 mg m^{-3}	1 µg m^{-3}	1 ng m^{-3}
1	2.2 µs	2.20 ms	2.2 s	36.67 min
2	12 µs	12.00 ms	12 s	3.34 hrs
5	0.12 ms	0.12 s	2 min	33.34 hrs
10	0.7 ms	0.7 s	11.67 min	8.1 days
20	3.8 ms	3.8 s	63.34 min	43.98 days

It can be seen from this that very small nanoparticles (e.g. 1 nm) coagulate rapidly even at low mass concentrations. However the outcome of this coagulation is still a nanoparticle, albeit a slightly large one. In turn this will coagulate and grow further.

For larger nanoparticles the coagulation half-life is much longer and therefore the growth is slower. While this mechanism will lead to rapid coagulation and therefore very short lifetimes of very small nanoparticles, larger nanoparticles will persist.

4.5.3 Deposition

Particles may be removed from the atmosphere by depositing onto floors, walls and other surfaces. The gravitational settling velocity of the particle is proportional to the diameter. Therefore airborne nanoparticles will fall out much more slowly than larger particles and gravitation settling will not be an effective removal process. This potentially would have the implication of causing higher, longer exposures for more workers.

In fact deposition of nanoparticles will be independent of orientation and will occur as they become trapped in the boundary layer on all surfaces including walls, ceilings and floors.

Hence a leakage of nanoparticles would end up widely dispersed and deposited on all surfaces throughout the work place. This contrasts with larger particles in which any leakage would tend to be more localised. Decontamination after a leakage of nanoparticles would therefore be much more difficult than after a leakage of larger particles and so the clean up processes may not be as effective. This could mean that small, widely dispersed deposits of nanoparticle material could remain attached to the surfaces for a much longer time periods leading to possible chronic exposure resulting in other routes such as dermal and ingestion exposure.

These behavioural aspects all relate to an airborne release of nanometre size particles. In principle this event could occur within the synthesis process of a gas phase or vapour phase production system. There would be much less likelihood of a release of this type in a liquid phase process.

4.5.4 Re-suspension

An alternative scenario is the re-suspension of nanoparticle material during powder handling or powder mixing activities in the recovery stage of the process. In this case the issue is whether or not a powdered nanoparticle material, which has been aggregated into bulk form, is likely to become re-suspended as a nanoparticle aerosol.

Re-suspension of aerosols from bulk powders is extremely complex and not easily predicted on a theoretical basis. Many factors can influence the possibility of re-suspension including particle size, particle shape, particle charge, the energy used in the activity which causes the re-suspension and moisture content of the powder.

Aerosol particles which contact one another generally adhere to each other and form aggregates or agglomerates. These particles tend to stick together because of attractive Van der Waals forces which act over very short distances relative to particle dimensions. Van der Waals forces would also act to keep a particle attached to a surface. The implication of this is that once attached (or agglomerated) small particles would be much more difficult to split up or re-suspend than large particles.

In the UK, the concept of dustiness has been applied to powders. Dustiness is an index of the relative ease by which powder materials can become re-suspended (HSE, 1996) and is assessed by agitating bulk materials and measuring the aerosol which is produced. Lyons and Mark (1994) assessed the dustiness of several materials including “fine” carbon black and silica flour. Results were assessed in terms of mass in the respirable and inhalable fractions. Both of these were found to be similar in dustiness to other common materials such as animal feeds and plaster. Information on dustiness as a function of particle number would be a more useful basis for comparing nanoparticle powders. We have been unable to find any reference which has systematically classified the dustiness of nanoparticle powders.

Maynard *et al* (2004) investigated the relative ease with which carbon nanotubes could be re-suspended. They used a fluidised bed to try to generate aerosols from bulk material. They concluded that it was very difficult to generate an aerosol from these materials.

On this basis it seems probable that some and possibly most nanomaterials, will not readily re-suspend into workplace air once they have been collected together in a bulk form. This is likely to be helpful in developing approaches to minimise airborne exposure arising from the handling of nanoparticle powders.

5. EXPOSURE TO NANOPARTICLES

5.1 NANOPARTICLE PRODUCTION PROCESSES

Nanoparticles, even from the same material, can be synthesised utilising a variety of methods. Different methods are used in order to optimise specific properties of the materials. These properties include, but are not limited, to size (diameter, length, volume), size distribution, symmetry, surface properties, surface coating, purity, ease of manipulation, yield and suitability for scaling up. Methods used for the commercial or deliberate manufacture of nanoparticles may be divided into four main groups. These are;

- Gas phase processes including flame pyrolysis, high temperature evaporation and plasma synthesis.

- Vapour deposition synthesis.

- Colloidal, or liquid phase methods in which chemical reactions in solvents lead to the formation of colloids.

- Mechanical processes including grinding, milling and alloying.

For all of these processes the recovery stage may be quite similar and is likely to comprise of mainly powder or slurry handling techniques.

5.1.1 Gas phase synthesis methods

Gas phase processes may be used to produce a wide range of materials. Most (but not all) nanoparticle synthesis methods in the gas phase are based on homogeneous nucleation of a supersaturated vapour and subsequent particle growth by condensation, coagulation and capture.

Gas phase synthesis methods have been reviewed by several authors including Kruis *et al* (1998) and Swihart (2003). Multiple approaches can be used to generate the supersaturated vapour dependant on the materials (precursors) used and the form of materials to be produced. In general, the formation of the vapour occurs within an aerosol reactor at elevated temperatures. The most straight forward method of achieving super saturation is to heat a solid and evaporate it into a background gas. This method is well suited for the production of metal nanoparticles in particular. By including a reactive gas such as oxygen, oxides or other compounds of the evaporated material can be produced. This method has also been used to prepare composite nanoparticles and to control the morphology of single component nanoparticle.

The precursor materials are introduced into the reactor as solids, powders, liquids or gases. In some cases, the precursors are nanoparticles, produced by a separate process. In the reactor, the precursors are heated and mixed with a carrier gas. The supersaturated vapour is produced by cooling or by chemical reaction or by some combination of these. Cooling may be induced by expansion, mixing with a cooler gas or by heat transfer to the surroundings. Chemical reactions used are usually decomposition reactions.

The supersaturated vapour nucleation process is initiated by the formation of very small particle embryos from the molecular phase. These nuclei subsequently grow surface growth mechanisms (heterogeneous condensation, surface reaction) and by collision and coagulation. Further collisions can result in the formation of loosely bound agglomerates or chain like, dendritic forms. The details of the overall process depend on the amount of available condensable gaseous materials, their thermodynamic and chemical properties as well as on the process conditions.

The methods can be categorised by the heating or evaporation process used (Kruis *et al;* 1998). These include;

- flame pyrolysis
- furnace flow reactors
- laser induced pyrolysis
- laser vaporisation
- thermal plasma
- microwave plasma
- sputtering
- laser ablation
- droplet evaporation

Flame pyrolysis methods are the basis of production for many of the existing industrial processes used to generate bulk quantities of nanomaterials such as carbon black and fumed silica. In flame pyrolysis, nanoparticles are produced by using the flame heat to initiate the chemical reactions. This is a relatively inexpensive, potentially high volume method which is used in the production of fumed silica (SiO_2) and ultrafine TiO_2. These materials are generated by the oxidation of titanium tetra chloride ($TiCl_4$) or silicon tetra chloride ($SiCl_4$) in a methane / oxygen flame. The disadvantage of this method is that it usually yields agglomerated particles. More details of these commercial processes (and the potential exposures arising) are given in Section 5.3 and Appendix 2. More complex products can also be synthesised using this method. For example, Zachariah *et al* (1995) described the production of iron oxide (Fe_30_4) particles embedded in $Si0_2$ host particles.

Furnace flow reactors are the simplest systems used to produce saturated vapour for substances having a large vapour pressure at intermediate temperatures. In these systems a crucible containing the source material is placed in a heated flow of inert carrier gas. Materials with low vapour pressure can be fed in as suitable precursors, such as organo-metallics or metal carbonyls into the furnace. This method has been used to produce nanoparticles such as silver (Ag), gallium (Ga), and galena (PbS). Maisels *et al* (2000) prepared composite nanoparticles of PbS with Ag by separate evaporation and condensation of the two materials followed by coagulation of oppositely charged particles. Ohno (2002) described the production of various composite nanoparticles including indium, lead (Pb), silicon (Si), germanium (Ge) and aluminium (Al).

In the laser pyrolysis technique, a flowing reacting gas is heated rapidly with an infra-red laser. The source molecules are heated selectively by absorption of the laser energy whereas the carrier gas is not. Decomposition of the precursors takes place due to the temperature increase and super saturation is created resulting in nanoparticle formation. This process has been used to produce Si nanoparticles from silane (SiH_4) (Canon *et al;* 1982) and Fe nanoparticles from iron pentacarbonyl ($FeCo_5$) (Majima *et al;* 1994).

Plasma reactors can also be used to deliver the energy required to cause evaporation or initiate chemical reactions. They can achieve temperatures of the order of 10,000°C. Powder feeds can also be decomposed by the plasma. The main types of plasma used are Direct Current (DC) plasma jet, DC art plasma and Radio-Frequency (RF) induction plasma (Young and Pfender, 1985). Commercial quantities of metal and metal oxide nanoparticles are produced using this method by QinetiQ Nanomaterials in what is described as “the UK’s first production facility dedicated to the volume production of specialist nanomaterials” (www.nano.qinetiq.com). More details of the QinetiQ process are given in Section 5.24.

Sputtering is a method of vaporising materials from a solid surface by bombardment with high velocity ions of inert gas e.g. Argon (Ar) or Krypton (Kr) causing an ejection of atoms. Sputter sources such as an ion gun or hollow cathode plasma sputter are normally used in the vacuum systems. Urban *et al* (2002) demonstrated formation of nanoparticles of a dozen different metals by magnetron sputtering of metal targets. This process needs to be carried out at low pressure which limits its effectiveness for further processing of nanoparticles in aerosol form and in the scaling up of this process.

Gas phase synthesis methods are considered to be able to produce improved specification and control in aspects such as particle size, crystallinity, degree of agglomeration, porosity, chemical homogeneity, purity and stoichiometry (Kruis *et al;* 1998) and are generally considered to offer good possibilities for scaling up to industrial level processes.

5.1.2 Vapour deposition methods

Chemical Vapour Deposition (CVD) methods are based on well established methods for the manufacture of semiconductors (Van Zant, 2000). These systems have conventionally been used to deposit thin films of silicon and other semiconductors on to semiconductor wafers. Vapour is formed in a reaction chamber by pyrolysis, reduction, oxidation and nitridation. Deposited film growth, in several stages beginning with nucleation as the first few atoms, deposit on the surface. These first atoms form islands which spread and coalesce into a continuous film. After this transition film is formed, growth continues until thicker film develops. Areas of growth on the wafer is controlled using various patterning processes (also known as photolithography or photomasking) in which deposition patterns are etched on to the surface layers of the wafers.

CVD methods have been used to produce nanoparticles from many different materials including TiO_2 (Nakaso *et al;* 2003), ZNO (Lie *et al;* 2004) and SiC (Honda *et al;* 2003). However the most important application is the synthesis of carbon nanotubes where CVD is considered to offer one of the most effective routes for scaling up to industrial production (Singh *et al;* 2003). This process is described in more detail in Section 4.2.2.

5.1.3 Colloidal methods

The third major group are the colloidal methods. These are well established “conventional” wet chemistry precipitation processes in which solutions of the different ions are mixed under controlled conditions of temperature and pressure to form insoluble precipitates. Colloidal methods provide a simple route to the synthesis of nanoparticles. This approach enables the relatively straightforward production of significant quantities of nanoparticle material at modest capital cost. As with other approaches, much of the recent emphasis has been on the development of more monodisperse particles with better defined shape.

The earliest reported colloids were metals. Preparation of metallic colloids dates back several centuries, but scientific investigation of their preparation on properties were first reported by Faraday (1857) in his experiments with gold. Development of colloidal theory, processes and methods have been ongoing since that time. Many comprehensive reviews are available including Hunter (1992), Hiemenz and Rajagopalan (1997), and Holmberg (2002) which describe this science in great detail. Nanomaterials produced by colloidal process include metals, metal oxides, organics, and pharmaceuticals.

Key papers by Brust *et al* describe the preparation of high quality nanometre sized gold particles (Brust *et al;* 1994; Brust *et al;* 1995). Other nanometer sized metal particles such as silver, (Murthy *et al;* 1997) platinum, iridium and palladium (Yee *et al;* 1999a,b) have been prepared by analogous routes.

An important and rapidly expanding sub-set of colloidal methods are sonochemistry methods, in which acoustic cavitation is used to control the process (Gedanken, 2004). In this process, molecular precursors undergo chemical reactions due to the application of ultrasound radiation. The main event in sonochemistry is the creation, growth and rapid collapse of a bubble that is formed in the liquid. High temperatures and high cooling rates accompany the collapse of the bubble and nucleation centres formed whose growth is limited by the rapid collapses. This method has been used to generate a wide range of nanoparticles including chalcogenides, metals and alloys including gold, cobalt and nickel as well as carbon and titania nanotubes.

Nanoparticles produced by these wet chemical methods can remain in liquid suspension for distribution and use or may be used as slurries. They may also be collected by filtering or by spray drying to produce a dry powder.

5.1.4 Attrition methods

The final group of methods are the mechanical attrition methods. In contrast to the previous three groups where nanoparticles were built "bottom-up" from individual molecules, in attrition methods nanoparticles are produced top down from larger particles.

Size reduction by grinding and milling is a very well established industrial process used to produce progressively finer forms of materials including minerals such as clay, coal and metals. Production rates of materials can be of the order of tonnes per hour. Production of the finest grades of material was previously referred to as micronising. Production of particles in the nanometer size range is referred to as ultrafine grinding (Mende *et al;* 2003) or nanosizing (Merisko-Liversidge *et al;* 2003).

The process involves wet milling in high shear media mills. Mende *et al* (2003) used a stirred media mill to produce suspensions of fused carborundum with a median per hole size of 50 nm. The milling chamber comprised rotating perforated plates. Alumina suspensions were also produced. Due to increasing particle – particle interactions in this process, it was necessary to stabilise the suspension by adjustment of the pH to prevent particle recombination.

Merisko-Liveridge *et al* (2003) used a similar process (described as Nanocrystal Technology) to produce nanometre size drug particles of poorly-water-soluble compounds. Again stabilisation was required to prevent recombination of the particles. Milligramme quantities of the drug were produced although it is understood that higher production rates can be achieved in commercial systems (www.elan.com). Particles with a diameter of 147 nm were produced by this method.

5.2 NANOPARTICLE PRODUCTION IN THE UK

5.2.1 Overview of nanoparticle production in UK

There are three types of organisations currently involved in the manufacture of nanoparticles in the UK, they are

1. University and other research groups;
2. New nanoparticle companies;
3. Existing chemical, pharmaceutical and refining companies.

In total there are over thirty-five UK research and university groups thought to be involved in nanotechnology in some form, of which perhaps no more than half were able to be identified from their preliminary web site information as being potentially involved in nanoparticle synthesis or application. Many of the nanotechnology / nanoparticle groups involve several university departments, utilising resources, ideas and skills from a variety of subject areas. There is also a great emphasis on collaborative research between research establishments and some have also joined together to form spin-out nanotechnology companies. At present, it is currently estimated that over 90% of nanotechnology companies in the UK are university spin-outs (ION, 2004). For example, Queens University, Belfast, the University of Ulster and various industries have joined together to form Nanotec NI, Northern Ireland's Nanotechnology research, development and exploitation centre.

The Interdisciplinary Research Collaboration (IRC) in Nanotechnology funded by EPSRC, BBSRC, MRC and the MoD as a collaboration between the Universities of Cambridge, Bristol and University College London forms one of the largest research groups working on nanoparticles. Other centres working in this area of nanotechnology include the University of Sussex, Bath and Manchester. A major area of research for many of these groups are carbon nanotubes primarily involving CVD synthesis methods described briefly earlier. For example, the University of Cambridge research interests include the application of fullerene based materials to nanoelectronics, properties of filled carbon nanotubes and so forth. Groups at the University of Sussex are working in several areas including nanotube production & modification, development of new ways of coating nanotubes with ceramics, polymers and fullerene chemistry manipulation. The University of Bath's research interests includes the development of special carbon structures and porous oxides and structured adsorbents, novel materials for reactive separations and catalysis.

Summary details regarding UK research and University group's nanotechnology interests can be found in Appendix 1.

The second group are the new nanoparticle companies. These have been identified from listings on websites such as www.nanoinvestasnews.com or from the ION report. Typically, they are companies who are involved in the manufacture and commercialisation of new nanoparticle materials or technologies (processes). A listing of these companies is provided in Table 5.1, along with details of the products and processes.

Additional details are provided for three companies, Thomas Swan & Co., Oxonica and Quinetic which are considered to be amongst the leading UK companies involved in the commercial production of (respectively) carbon nanotubes, nanodots and "other" nanoparticles. No UK commercial manufacture of nanowires were identified.

The third group are the existing chemical and pharmaceutical companies. These can be divided into two categories:

1. Companies such as DeGussa (carbon black), Chengyin (ultrafine titanium dioxide) and Cabot (fumed silica), who manufacture bulk materials in gas phase processes (flame pyrolysis).

2. Existing chemical and pharmaceutical companies such as ICI, Syngenta and GSK who manufacture bulk materials primarily through wet chemistry (colloidal) process.

Through websites and other contacts, we have obtained details the manufacture of bulk materials through gas phase processes in existing processes. These are discussed in Appendix 2.

Within the time frame of this review we have been unable to obtain much information relating to the bulk manufacture of chemicals. A full review of all of the chemical processes and products is clearly beyond the scope of this review. Many of the details are in any case commercially confidential. It is expected though that with these companies, and within other similar companies there will be significant activity focussed on development of materials which are smaller, more regular in shape etc than the previous materials. Many of these will be liquid based syntheses. Evaluation of the exposure and control issues in these processes should be picked up by the current regulatory processes and inspection regimes.

Table 5.1 UK companies involved in the manufacture of nanoparticles

Company name	Overview	Processes
Adelan Ltd www.adelan.co.uk	A small solid oxide fuel cell "spin out" company originating from the materials research developments from Birmingham and Keele Universities.	
Dupont Air Products Nanomaterials L.L.C. www.nanoslurry.com	Joint venture Du Pont and Air Products Develop and manufacture colloidal polishing slurries for use in the semi-conductor industry. For example, Ascend™ OX-200 Colloidal Silica Slurry, an ammonia stabilized colloidal silica sol that has an average particle size of 40 nanometers.	Colloidal silica manufacturing facility
Johnson Matthey www.matthey.com	Nanopowders: Colour and Coatings Division: manufacture of colours and surface coatings for a wide range of industries. Various UK facilities Precious metals division: Produce wide range of platinum group metal products. Also developed proprietary technology for coating platinum group metals on a wide range of substrates. Platinum fabrication facilities are in Royston.	Colloidal processes
Liquids Research Ltd www.liquidsresearch.com	Manufacture of ferrofluids and other magnetic composite materials based on ferrite and metal particles. Ferrofluids consist of very small magnetic particles held in suspension in a carrier liquid by a surface active layer. Magnetorheological fluids are stable suspensions of magnetically polarisable micron sized particles suspended in a low volatility carrier fluid, usually a synthetic hydrocarbon.	
Nanoco Technologies www.nanoco.biz	Nanopowders Production of nanoparticles and quantum dots for security/authentication, life science and electronic applications. Batches of cadmium selenide and cadmium selenide particles coated with zinc sulphide or cadmium sulphide, sized to customers' required specifications NanoDots supplied either as dry powders, dissolved in clear solvent solutions or suspended in waxy solids to enhance stability for long-term storage.	Unique, patented single source precursor ('one pot') manufacturing process: Owns E.U and U.S. patents protecting the company's proprietary method for the design and syntheses of mono-dispersed customized nanoparticles including compound semiconductor 'quantum dots', metal oxide and precious metals.

Nanomagnetics Ltd. www.nanomagnetics.com	Design and manufacturers advanced magnetic particles (called DataInk$^{\text{TM}}$) for the magnetic media manufacturing industry. Produce a powder which the media manufacturers mix with a resin and coat flexible substrates to make tape and discs for magnetic recording.	
Oxonica, Ltd. www.oxonica.com	Nanopowders Cerulean International, Oxonica's wholly owned subsidiary, created to commercialise *Envirox*, a next generation nanocatalyst for fuel applications. *Optisol* is an extremely photostable UV absorber was developed in association with the University of Oxford. Also developing applications for diverse industry sectors including bio-diagnostics and the security market. Co-operating with the US-based nanotechnology Evident Technologies. Evident are one of the only organisations commercially manufacturing a range of quantum dot materials (*Evidots*) - precision semi-conductor nanocrystals.	Colloidal processes Details of patents can be found on: http://www.oxonica.com/about_nanomaterials/patents.html
QinetiQ Nanomaterials Ltd.(QNL) www.nano.qinetiq.com	Nanomaterials. QNL fully owned subsiderysubsidiary of QinetiQ Group. Produce dry powders in bulk quantities, for example, various metal nanoparticles (i.e. ultrafine aluminium, copper and cobalt), various metal oxides (i.e. zinc and copper).	Gas phase production technology used
SmartBead Technologies Ltd www.smartbead.com	Microparticles with intrinsic barcodes	Relatively conventional optical lithography
Tetronics Ltd www.tetronics.com	Nanopowders Has a wide range of technologies for the production and processing of powders in general and for nanopowder production specifically. Processes have been used to produce particles with average particle size between 10 - 60 nm and specific surface area between 15 - 40 m^{2}g. Examples of nano and novel materials produced include zinc oxide, aluminium nitride, silicon nitride, silicon carbide, mixtures of silicon carbide and silicon nitride, magnesia, alumina, zirconia, titania, zirconium silicate, calcium chloride, carbon black.	DC Plasma arc technology Developed a range of techniques for the production of nanomaterials based around single plasma torches, graphite electrode systems or Tetronics own unique Twin Torch process.
Thomas Swan & Co. Ltd www.thomas-swan.co.uk	Nanotubes Has UK's first commercial manufacturing process for high-purity single-wall carbon nanotubes. Product name 'Elicarb™ SW'.	Chemical vapour deposition (CVD) method.

5.2.2 Thomas Swan & Co

Thomas Swan and Co (www.thomas-swan.co.uk) is the leading commercial producer of carbon nanotubes (CNT) in the UK. Their new facility, developed in collaboration with Cambridge University (Department of Materials Science) is described as the UK's first commercial manufacturing process for high purity single wall CNTs. The plant uses an injection chemical vapour deposition process which is understood to be an industrial scale of the method reported by Singh *et al* (2003), described earlier. In this process, precursors are injected into a two stage furnace and the nanotubes are grown in quartz substrates. After synthesis they are removed by mechanical means under controlled conditions.

The main commercial product is Elicarb™SW, described as purified single wall CNTs with an average diameter of less than 2 nm and an average length in the micrometre range. It is formulated as a dry powder and is advertised as being available in packs of 1gram up to 1 kilogram at a price of £200 per gram.

Other Elicarb^{TM} products including multiwalled CNTs are available or will be available in due course. The company also offers to produce CNTs tailored to clients specific requirements.

5.2.3 Oxonica

Oxonica (www.oxonica.com) is one of the UK's leading producers of nanodots (also known as quantum dots or nanocrystals). Oxonica specialises in 'wet chemistry' routes to nanomaterials employing traditional colloidal chemistry and organometallic processes (Green *et al;* 2002). They have expertise in growing semiconductor quantum dots, specifically materials, such as cadmium selenide, CdS, as well as metals such as cadmium sulphide gold.. Their process controls the surface and reaction routes to generate specific sized materials, which are soluble in specific solvents.

Oxonica's technology is protected by intellectual property and there are currently 22 filed patent details, available on its website. The technology has direct applicability to a number of markets where dispersion and/or manipulation of optical properties are important. These include catalysis, life sciences, environmental sciences, IT and telecommunications, pigments /printing, polymers, ceramics and cosmetics.

Currently the company has three main nanoparticle products. Envirox is a novel nanocatalyst technology for diesel fuels. It is based on an oxidation catalyst widely recognised as a combustion improver and used for emissions control. It has been re-engineered to allow it to be used as a fuel-borne catalyst leading to a cleaner, more complete burn within the combustion chamber. This results in significantly improved fuel efficiency, reduced carbon deposits in the engine, and lower emissions. No engine modifications are required to use the product, it has no impact on lubricant performance, and the dose rate is low.

Oxonica's patented process modifies the structure of the T_1O_2 or zinc oxide to create Optisol, an extremely photostable UV absorber which works without the concurrent formation of free radicals, highly reactive chemical species which are implicated in skin ageing and cell damage.

In addition Oxonica is co-operating with the US-based nanotechnology company Evident Technologies in the manufacture and distribution of Evidots. Evident are one of the only organisations commercially manufacturing a range of quantum dot materials - precision semiconductor nanocrystals. By manipulating the size of the particles it is possible to engineer their wavelength, absorption resonance and the semi-conductor band gap.

Oxonica offers a range of novel nanocrystalline luminescent materials. These materials have been engineered to emit in a very narrow wavelength range, giving clear, clean colours. Oxonica is able to manipulate the particles to achieve different colours with no requirement to control the particle size. The materials are based on non-toxic inorganic compounds and are therefore highly stable. There are many applications for these products including fluorescent labelling, covert marking, flat panel displays and solid state lighting.

5.2.4 QinetiQ

QinetiQ Nanomaterials Ltd (www.nano.qinetiq.com) working in conjunction with Tetronics (http://www.tetronics.com) have developed plasma synthesis techniques which can produce commercial quantities of metal and metal oxide nanoparticles. Their site is described as the UK's first production facility dedicated to the volume production of specialist nanomaterials. The company has two production rigs which are capable of producing up to several kilogrames of nanomaterials per hour.

In the QinetiQ process pre-cursor materials are fed into a high-temperature plasma (typically in the temperature range of 4,000-9,000°C). The feed stock material is vaporised on contact with the plasma and is carried away from the hot zone on a gas stream. The vapour is rapidly quenched which causes the material to be condensed and solidified to form nanometre size powder particles. These are carried through to a collection system, based on a bag filtration system. After synthesis the bag filter system is reverse pulsed and the form of material is collected into a hopper. The process is capable of producing dry powders in bulk quantities to a consistent quality and can produce metals to a high purity. Pure metals, passivated metals (metals with a thin oxide layer), oxides, nitrides and other alloys can be produced using this method. Processing conditions can be varied to control particle size, size distribution and composition. Materials that have been produced include alumina, zirconia, yttria, zinc oxide, seruim oxide and titanium oxide. A range of other materials including nitride and carbides can be formed.

Typically these are described as loosely aggregated nanometer particles. The primary particle size is 100 +/- 50 nm. Depending on the details of the process used, the primary particles may be almost spherical or of more irregular shape. The size of the aggregates is typically described as from 5-200 microns.

A summary of products from QinetiQ is shown in Table 5.2

Table 5.2 Products available from QinetiQ

Material	Form
Aluminium	Passivated, metal core with oxide layer Vapour phase condensed spherical particles (agglomerated) 100+/-50 nm agglomerates (soft aggregates) 2-200 μm
Copper	Pure metal Vapour phase condensed spherical particles (agglomerated) 100+/-50 nm agglomerates (soft aggregates) 2-200 μm
Cobalt	
Zinc	
Silver	
Tungsten	
Molydenum	
Zinc oxide	Irregularly shaped particles with primary particle size 30-100 nm
Copper oxide	Irregularly shaped particles with primary particle size 10-100 nm
Zirconia	
Yttria	

QinetiQ also offer speciality materials on a development basis. These include doped materials with dopant added to oxides, alloys of high purity, layered materials and mixed or structured oxides.

5.3 EXPOSURES IN NANOPARTICLE PROCESSES

In all nanoparticle production processes there is a potential for exposure to occur at both the synthesis and recovery phase of the process. The nature of the exposure, the likely level and the probability of exposure will differ according to the specific process and the stage of the process. Similarly, the optimum strategy to control exposure, and the efficacy of the control methods used will differ depending on the specific process. Table 5.3 summarises the potential risks of exposure in nanoparticle production processes.

Table 5.3 Potential risks of exposure in nanoparticle production processes

Synthesis processes	Particle formation	Potential inhalation risks	Potential dermal/ingestion risks
Gas phase	in air	Direct leakage from reactor Product recovery Post recovery processing and packing	Airborne contamination of workplace Handling of product Cleaning/maintenance of plant
Vapour phase	on substrate	Product recovery Post-recovery processing and packing	Dry contamination of workplace Handling of product Cleaning/maintenance of plant
Colloidal	liquid suspension	Drying of product (processing and spillage)	Spillage/contamination of workplace Handling of product Cleaning/maintenance of plant
Attrition	liquid suspension	Drying of product (processing and spillage)	Spillage/contamination of workplace Handling of product Cleaning/maintenance of plant

In gas-phase processes, nanoparticles are formed as an aerosol inside a reactor vessel. Hence there are potential risks of inhalation exposure in the event of leakage of product from the vessel, particularly if the system operates at positive pressure. The nature of the aerosol released would be dependant on the point in the process at which leakage occurs. In the initial stages of the process, primary nanoparticles could be released. Later in the synthesis process a more aggregated aerosol (still of nanoparticles) could be released. Ultimately particles in the form of loosely bound agglomerates could be released into the workplace air.

Exposure by inhalation could also occur during product recovery. The recovery method will differ depending on the process. In some gas-phase processes, product nanoparticles are collected in bag filters. These are reversed pulsed and the product nanoparticles recollected into a hopper or other receptacle. Ineffective filter systems could result in escape of product into the working environment, particularly where recirculation into the workplace air occurs.

During recovery stage and in any further processing or packing the particles will be in the form of an agglomerated bulk powder. The likelihood of exposure by inhalation will be dependent on the details of the process and the characteristics of the product. In particular the extent to which it can become re-suspended in the air as discussed earlier in Section 4.5.4.

In gas-phase processes, there are potential risks of dermal (and ingestion) exposure by touching surfaces contaminated by airborne releases, handling of product during recovery and processing or packing and during maintenance or cleaning of the plant and workplace.

In vapour-phase processes, particle formation is on a substrate so direct release of particles during synthesis into the workplace air is unlikely. Product recovery is likely to involve mechanical removal of particles from deposition substrates. This could be manual or automated. Depending on the level of energy used, this could result in re-suspension of product into the air. It is very unlikely that this would be in the form of discrete nanoparticles but could be agglomerated particles. Any post-recovery processing and packing is likely to be similar to gas-phase processing, with similar risks of exposure. Scenarios for dermal and ingestion exposure will be similar to gas-phase processes.

In colloidal and other chemistry processes particle formation is in liquid suspension so direct exposure by inhalation is unlikely during the synthesis stage. In some of these processes, product recovery is by spray drying in which the product is sprayed into an evaporation chamber. In these situations, airborne exposure is possible in the event of leakage although it is unlikely to be to primary single nanoparticles but rather to agglomerates of nanoparticles. Spillage of liquid product in the workplace, followed by evaporation and cleaning could result in airborne dispersion and inhalation exposure. Again this is more likely to be to agglomerated materials.

In these processes, dermal (and ingestion) exposure could occur as a result of spillage in the workplace. Exposure could be directly to the suspension or to dried material. Handling of the product during recovery/packing and maintenance and cleaning could also result in dermal exposure.

The risks of inhalation, dermal and ingestion exposures would be similar in attrition processes to colloidal processes but would differ in detail.

5.3.1 Exposures in new nanoparticle processes

We were unable to identify any studies which have directly investigated exposure in new nanoparticle processes in the UK.

Maynard *et al* (2004) carried out a laboratory based study to evaluate the physical nature of the aerosol formed from single-walled carbon nanotube material (SWCNT) during mechanical agitation. This was complemented by a field study in the United States in which airborne and dermal exposure to SWCNT was investigated while handling unrefined material. Details of the field study are provided below.

Two techniques for producing SWCNT were investigated. These were laser abalation and high-pressure carbon monoxide (HiPCO). Both of these processes lead to the production of a very low density material comprised of nanometre-diameter catalyst metal particles, CNTs and other forms of elemental carbon which are manually recovered prior to further processing.

Measurements of unprocessed airborne nanotube exposures were made at four faculties where SWCNT material was removed from production vessels and handled prior to processing. The sample locations were as follows:

1. Laser ablation facility - sampling carried out during material removal and clean-up. A vacuum cleaner, fitted with a HEPA filter, was used for clean up in the enclosure. This was later discovered to have been incorrectly fitted which led to re-suspension of dust when the vacuum cleaner was used.

2. HiPCO process removal simulation – removal of SWCNT was simulated by pouring previously generated material between two buckets normally used for collecting nanotubes. Sampling occurred during filling, pouring and cleanup activities. Cleanup was undertaken using a vacuum cleaner with a low efficiency filter.

3. Laser abalation process removal simulation – due to space constraints the collection chamber for the laser process was removed from the production system and placed into the clean-air enclosure for powder removal. Sampling was carried out while the chamber was open, the material removed and the area cleaned. A vacuum cleaner was used during the clean up which was positioned outside with the hose extending in.

4. HiPCO process - Collection chamber was removed from the production system and placed into the clean-air enclosure for powder removal. Sampling was carried out during the opening of the chamber, removal of material, cleaning of area and dismantling of the enclosure. A vacuum cleaner was used during the clean up which was positioned outside with the hose extending in.

The filter samples were taken over the time period the workers spent in the enclosure, which was typically about half an hour.

Table 5.4 shows the estimated nanotube concentrations for the personal air and glove samples for each of the locations monitored. The samples were analysed for iron and nickel as surrogates for total nanotube product mass, thus providing a low limit of detection while discriminating between SWCNT and other airborne material. SWCNT mass was estimated for each sample assuming a combination of nickel and iron particles constituted 30% of the mass of the material.

Table 5.4 Exposures in carbon nanotube manufacture

Sampling site	Personal air samples		Glove samples
	Sampled volume (m^3)	Estimate conc. (µg/ m^3)	Estimated nanotube (µg)
1	0.139	0.7 (Ni)	217
2	0.079	36.29 (Fe)	3705
3	0.096	9.86 (Ni)	863
4	0.132	51.73(Ni) 52.73 (Fe)	6020

Estimates of nanotube concentrations ranged from 0.7 to 53 µg/ m^3. Filter samples indicated that many of the particles may have been compact, rather than having an open, low-density structure more generally associated with unprocessed SWCNT. Air measurements will have included large airborne clumps of material that were not respirable. However these particles, together with surface deposits, would have posed a dermal exposure risk.

Estimates of the SWCNT material on the individual gloves ranged from 217 µg to 6020 µg, with most of the material appearing on the parts of the gloves in direct contact with surfaces (inner surfaces of fingers and palms). Although the use of gloves and PPE will minimize dermal exposure during handling of this material, the possibility for large clumps to become airborne and remain so for long periods may lead to dermal exposures in less well protected regions.

Measurements indicated higher air and glove SWCNT concentrations for HiPCO material. These higher levels may have been associated with the lower density, 'fluffier' HiPCO material becoming more easily airborne as large clumps of material.

Inspection of the area samples showed relatively few particles on the samples. Samples from HiPCO SWCNT contained a small number of particles, on the order of 100µm to 1mm in diameter, having relatively open nanorope structures. However, most micrometer-sized particles in the analysed HiPCO sample appeared to have a compact structure, with very few nanotubes apparent. In contrast, micrometer-sized particles from the laser ablation process were more clearly comprised of nanoropes. No evidence of millimeter-sized nanotube material clumps were found in aerosol samples from laser-ablated material.

While laboratory studies have indicated that with sufficient agitation SWCNT material can release fine particles into the air, the aerosol concentrations generated while handling unrefined material in the field at the work loads and rates observed were low. In none of the field studies is there any indication that handling the nanotube material leads to an increase in the number concentration of fine particles, suggesting that released particles tend to be larger then 1µm or so in diameter. The findings agreed with lab data indicating that submicrometer particles are not readily released at low levels of agitation. More energetic processes would be expected to release higher concentrations of nanotube aerosol. There is some question over whether the use of a vacuum cleaner during the cleanup led to large releases of small nanotube clusters, or whether the observed particles originated from the device itself. This is clearly an area requiring further investigation but at this stage it would seem prudent to use HEPA-filtered cleaners with correctly fitted filter units to prevent the potential release of large nanotube number concentrations.

Maynard *et al* (2004) research provides an initial indication of the propensity with which unprocessed SWCNT forms an aerosol during handling. Overall, very little is known on how likely inhalation and dermal exposure will be during the handling and manufacturing processes of nanoparticles. As nanotechnology is continuously producing new materials in the ultrafine range, existing data from industries where ultrafine particles are produced may help in the estimation of likely levels of exposure.

5.3.2 Exposures in existing nanoparticle processes

Existing gas phase manufacturing processes are summarised in Table 5.5. Other process in which exposure to incidentally generated nanoparticles may occur are summarised in Table 5.6

Table 5.5 Existing gas phase manufacturing processes

Product	Process	UK sites
Fumed silica	Flame aerosol synthesis	No
Carbon black	Flame aerosol synthesis	Yes
Ultrafine titanium dioxide	Flame aerosol synthesis	No
Precious metal blacks		Yes
Fine nickel powder	Gaseous	Yes

Table 5.6 Summary of incidental processes generating ultrafine aerosols

Process	Generation by
Thermal spraying and coating	Heat
Metal production / refining	Heat
Welding	Heat
Soldering	Heat
High speed metal grinding	Abrasion and attrition

Details of these processes and the main studies which have investigated exposures in them are provided in Appendix 2. This information is summarised below in Table 5.7.

Table 5.7 Summary of aerosol exposure by industry, process and activity

Industry	Measurements (range)	Activity	Ref
Carbon Black	3470-49900 particles/cc air	Bagging	Wake (2001)
	4210-22500 particles/cc air	Bagging	
	C.black inhalable <LOD – 37 mg/m^3	Manufacture	Gardiner *et al* (1992&1996)
	C. black respirable <LOD–7 mg/m^3	Manufacture	van Tongeren *et al* (2000a & 2000b)
	Agglomerated particles		
		Manufacture	Kuhlbusch *et al* (2001)
	General inhalable 0.9 – 57 mg/m^3	Use – rubber	
	C.black inhalable 0.001 - 0.6mg/m^3	Use- toner man	
	General – inhalable 0-30 mg/m^3	Use – rubber	IARC (1996)
			IARC (1996)
			Meijer *et al;* (1998);
			Dost *et al*; (2000);
	C.black inhalable <LOD- 9.5	Various	Vermeulen, personal communication
	General inhalable <LOC-23	Various	IARC
Nickel powder	3670-21200 particles/cc air	Bagging	Wake (2001)
Precious metal blacks	23106-70745 particles/cc air	Sieving	Wake (2001)
	21087-61074 particles/cc air	Sieving	
Titanium dioxide	4150-16615 particles/cc air	Bagging	Wake (2001)
	4998-21167 particles/cc air	Dust prep	
	‘high’	Milling, packing	Fryzek *et al;* (2003)
	‘lower’	Adding treatments	
	‘minimal’	General labourers	
	10-400mg/m^3	Grinding	Elo *et al ;* (1972)
Pharmaceutical	0.9 mg/m^3	Drum dumping	Naumann and Sargent, (1997)
	1.2 mg/m^3	Dumping from bags	
	0.8 mg/m^3	Scoping from drums	
	0.6 mg/m^3	Filling drums	
	0.2 mg/m^3	Bin transfers	
	0.3 mg/m^3	Digging centrifuge	
	2.3 mg/m^3	Milling	
	2.7 mg/m^3	Tray dumping	
	0.1 mg/m^3	Film coating	
	0.8 mg/m^3	Sieving	
	0.9 mg/m^3	Granulating	
	0.08 mg/m^3	Compressing	
	0.01 mg/m^3	Packaging	
	0.01 mg/m^3	Sampling	
	0.05 mg/m^3	Encapsulating	
Thermal coating	3590-11200 particles/cc air	Wire coat	Wake (2001)
	2820-11300 particles/cc air	Auto	
	11700-25900 particles/cc air	Hand	
	average 24-hr mass conc. of particles smaller than 3.2µm in aerodynamic diameter - 112.7 µg/m^3	Automotive heat process	Sioutas (1999)
Zinc refining	12000-24000 particles/cc air	Sintering	Wake (2001)
	28000-54000 particles/cc air	Sintering	

	3400-54000 particles/cc air	Prop	
	20000-340000 particles/cc air	Prop	
	42000-680000 particles/cc air	Ref top	
	56000-100000 particles/cc air	Ref floor	
Steel foundry	118000->500000 particles/cc air	Fettling	Wake (2001)
	228000-484000 particles/cc air	Fettling	
	148000-343000 particles/cc air	Moulding	
	157000-414000 particles/cc air	Moulding	
	13.5 mg/m^3	arc gouging	
	4.6 mg/m^3	burning	
	1.3-2.4mg/m^3	fettling	
Aluminum smelter	3700 ug/m^3	Rotary furnace	Healy *et al;* 2001
	2100ug/m^3	Sloping hearth	
	2200ug/m^3	Induction	
	2400 ug/m^3	Reverber/ holding	
	800 ug/m^3	Casting	
Welding	117649->500000 particles/cc air	MIG	Wake (2001)
	129121->500000 particles/cc air	MIG	
	68792-278170 particles/cc air	MMA	
	65512-268601 particles/cc air	MMA	
	Average 24-hour mass concentrations of particles smaller than 3.2µm in aerodynamic diameter 167.8 µg/m^3	Automotive welding	Sioutas (1999)
Hand soldering	11752->500000 particles/cc air	Tinning	Wake (2001)
	7642-429068 particles/cc air	Tinning	
High speed metal grinding	average 24-hour mass conc. Of particles smaller than 3.2µm in aerodynamic diameter - 103.9 µg/m^3	Grinding	Sioutas (1999)
	mass median diameter		
	Particle size - 4.22nm to 20.5µm	Grinding	Zimmer and Maynard (2002)

6. CONTROL OF NANOPARTICLES

6.1 INTRODUCTION

Using chemicals or other hazardous substances at work can potentially put people's health at risk. In the UK, the law requires employers to control exposure to hazardous substances to prevent ill health. The framework by which compliance can be achieved and demonstrated is the Control of Substances Hazardous to Health Regulations 2002 (COSHH) (HSE, 2002). This is a scheme of good health and safety management involving eight basic measures that set out in a simple step-by-step approach to help assess risks, implement any measures needed to control exposure and establish good working practices. The major elements in this approach are:

- Identify the hazard,
- Assess the risk,
- Prevent or control the risk,
- Evaluate the effectiveness of control measures.

At the current time there are some major uncertainties that limit the extent to which adequate assessment of the risks arising from exposure to nanoparticles can be made. Risk assessment requires an understanding of the toxic potential of a material and the levels of exposure which are likely to arise in various scenarios where it is used. It is clear from the foregoing that nanoparticles are not a single group of objects but a multiplicity of shapes, sizes and compounds. A unifying feature of nanoparticles is that they will be smaller than the materials which they replace, and will have larger surface area per unit mass. These parameters are known to increase the toxic potential of a material. (Tran *et al;* 2000).

Little toxicological assessment of these materials has been carried out (Fraser *et al*; 2004). It is clear from this review that little is known concerning the exposures of those working with these materials. There is a wider issue in that there is no unified view as to the appropriate metric by which exposure might be measured. There is some reassurance that the limited studies which have been carried out do not suggest that there are high airborne concentrations of nanoparticles in workplaces where they are manufactured (although these tend not to take account of agglomerated particles). However, it is it not easy to be confident that in all workplaces where these materials are being manufactured an adequate assessment of the risks has or will be made. Nevertheless, assessment of risk have to be made based on the best available information, and control strategies will have to be developed based on these assessments.

Strategies to control exposure to nanoparticles may include:

- Total enclosure of the process
- Partial enclosure with local exhaust ventilation
- Local exhaust ventilation
- General ventilation
- Limitation of numbers of workers and exclusion of others
- Reduction in periods of exposure
- Regular cleaning of wall and other surfaces
- Use of suitable personal protective equipment
- Prohibition of eating and drinking in contaminated areas

Choices for each of these will need to be made based on some understanding of the differences between nanoparticles and larger particles.

6.2 EXPOSURE BY INHALATION

6.2.1 Engineering control

For air velocities prevailing in workplaces, airborne nanoparticles can be considered as having no inertia. They will therefore behave in a similar way to a gas and if not fully enclosed will diffuse rapidly and will remain airborne for a long time. Because of their high diffusion velocity, these particles will readily find leakage paths in systems in which the containment is not complete. Engineering control systems designed for use to control nanoparticles such as enclosures, local exhaust ventilation (LEV), fume hoods and general ventilation therefore need to be of similar quality and specification to that which is normally used for gases rather than for particulate challenges. These systems do exist and are in common use in the chemical and other industry. Like all such systems effective performance of these systems will be highly dependent on appropriate use and maintenance.

Engineering controls are widely used to reduce exposure to welding fume. A variety of methods are recommended including general ventilation, LEV, fume hoods and on-gun extraction (HSE, 1990). The level of protection provided by these methods is considered to be quite variable and dependent on issues previously mentioned such as maintenance and worker behaviour. Engineering controls of this type are also used in the carbon black industry but as indicated earlier, significant exposure in this industry still occurs.

We have identified no relevant research that has specifically sought to evaluate the effectiveness of engineering control systems against new nanoparticle challenges. While most of these systems can in principle be used to control exposure, they do not always do so. There is no reason to expect that application of these methods to new nanoparticle generation processes will result in better control than that previously demonstrated in micro-scale powders and in gases.

6.2.2 Filtration

Filtration plays an important role in the control of exposure to airborne particles. High Efficiency Particulate Arrester (HEPA) filters are used in engineering control systems to clean the air before returning it to the workplace. These filters are usually referred to as mechanical filters.

Filtration theory is well understood and has been extensively described by several authors (e.g. Brown, 1992). As an aerosol penetrates through a filter, the trajectories of the particles deviate from the streamline due to various well understood mechanisms. As a result, particles may collide with the filter elements (fibres) and become deposited on them. The mechanisms include diffusion, interception, initial impaction and gravitational settling. Electrostatic forces can also play a role in some filter types.

For particles less than 100nm, Brownian diffusion is the dominant mechanism (Lee and Mukund, 2001). Filtration efficiency due to Brownian diffusion increases as particle size decreases. Brownian diffusion is caused by collisions between particles and the air molecules to create random paths which the particles follow. The random motion increases the probability of a particle contacting one of the filter elements. Once the particle is collected onto a surface it will adhere to it due to the Van der Waals forces. Therefore filters are likely to be good collectors of nanoparticles.

Current methods for certification of HEPA filters and for respirator filters do not routinely require testing at particle sizes in the nanometre size range. Internationally recognised standards for HEPA filters (DOE, 1998) require that the filter is challenged with an aerosol with a mass median diameter of 300nm and that the particle collection efficiency is greater than 99.97%. Three hundred nanometers is considered to be a much more penetrating aerosol for these filters than nanometre size particles due to the decrease of Brownian diffusion at this particle size. Similarly European Standards for respirator filter cartridges (CEN, 2001a) and for filtering face pieces (CEN, 2001b) require that these systems are tested against sodium chloride aerosols with a mass median diameter of 300nm. Again this is based on an expectation that this would be the most penetrating size.

However some authors have suggested that penetration of nanometer particles through wire screens (filters) can deviate from the classical penetration models if the effect of thermal rebounds is significant. Wang (1996) used a modified penetration model including the effect of “thermal rebounds” to compare with the experimental results of Ichitsubo *et al* (1996). He found good agreement using model parameters derived from literature. Both experiment and theory suggested significant thermal rebounds and increased penetration for particles smaller than 2nm. Similar results have been reported by Otani (1995) who found that the particle rebound may increase the penetration for platinum nanoparticles through circular diffusion tubes when the particles are smaller than 2nm.

Little work has been done to quantify the performance of filters against particles in the nanometre size range. It is still widely accepted, that with diffusion the dominant mechanism and the efficiency of filters will be high.

6.2.3 Use of Personal Protective Equipment (PPE)

Use of PPE such as respirators and air fed devices may be used (as a final option) as a method of control for any airborne hazard. All of these devices depend on filtration as a means of cleaning the air prior to it being breathed by the worker. The discussion relating to filtration applies equally here. It is probable, for all but the smallest nanoparticles (<2nm) that the filtration efficiency will be high. It was not possible to identify any relevant research which has demonstrated this.

It is well recognised however that the determining factor which governs the effectiveness of respiratory protection equipment (RPE) against particulate challenges is not absolute penetration through the filter, but rather face-seal leakage which bypasses the device. Face seal leakage is dependent on many factors including the fit of the mask to the face, duration of wearing, work activity etc. Since it is expected that nanoparticle aerosols will have high mobility, it is possible that enhanced leakage will occur although no more than might be expected for a gas. No relevant research to quantify this has been identified.

6.3 DERMAL EXPOSURE

Issues relating to dermal exposure have only relatively recently come to prominence in occupational hygiene. Based on our understanding of the various processes by which nanoparticles can be synthesised there seems to be a strong possibility of dermal exposure occurring, most likely in the later stages of the process i.e. recovery or resulting from surface contamination. There is some evidence that dermal exposure to nanoparticles may lead to direct penetration of nanoparticles into the epidermis and possibly beyond into the blood stream. Therefore, it may be necessary to introduce control to exclude or limit the level of dermal exposure likely to occur.

As for inhalation exposure, COSHH provides a framework by which a strategy to prevent or control dermal exposure can be developed. However, it is acknowledged that prevention of dermal exposure is not covered so well in the guidance associated with COSHH.

As with control of exposure by inhalation, the first approach is enclosure of the process. This should certainly be achievable as powder handling processes can be enclosed successfully. However in practice, particularly with products or processes which are in development, the main emphasis is on investment and expenditure at the synthesis end of the process. This is likely to limit the expenditure on sophisticated control and automation processes to deal with what will be perceived as relatively mundane tasks such as harvesting and packing of nanomaterials.

In any case even where such processes are in place, the requirements for attention to breakdowns, maintenance etc means that the possibility of dermal exposure cannot be excluded at all times. In these and other instances protection against dermal exposure typically consists of the use of Skin Protective Equipment (SPE) i.e. suits, gloves and other items of protective clothing.

Even for powders in the macro scale, it is recognised that SPE is very limited in its effectiveness to reduce or control dermal exposure. Based on current understanding (Schnieder *et al;* 2000) multiple processes contribute to dermal exposure, and the relative ineffectiveness of SPE. In addition to the classical view that the failure of SPE results from direct penetration or permeation of an agent through the material from which the equipment is constructed, other process include transfer of substances by direct contact between surface, skin and outer respectively inner clothing or gloves, and redistribution of substances between compartments of the same type, e.g. redistribution of contaminants from one part of the skin contaminant layer to another as a result of touching the face with contaminated fingers.

Current European testing for certification of PPE against dermal exposure only takes account of permeation or penetration. Although recently, new tests have been proposed which take account of the other human factors based on simulations (Brouwer *et al;* 2004). Since it is likely that nanoparticles which escape into the workplace will become widely dispersed and will have high surface area, it is likely that the human factor element will be even more critical than for macrosize particles. In this case, it is quite likely that SPE will be less effective against nanoparticles than against macro size particles. It is also quite likely that direct penetration of nanoparticles through the material from which the protective clothing is made will be higher than for macrosized particles.

We have been unable to identify any relevant research work which has looked at either the efficacy of SPE against direct penetration of nanoparticles, or the impact of nanoparticles on the probability of failure of SPE due to human factors. No information on these issues was available from any of the manufacturer’s websites.

6.4 INGESTION EXPOSURE

Understanding about exposure by ingestion in the workplace is not currently well developed. It is considered that ingestion exposure in the workplace results primarily from hand-to-mouth contact. It follows that strategies which tend to reduce dermal exposure in the workplace will also tend to reduce exposure by ingestion. The converse of this is also true. At this point in time we have identified no relevant research which has successfully quantified exposure to nanoparticles by ingestion in the workplace or the effectiveness of strategies to reduce this exposure.

7. POTENTIAL AND PREDICTED NUMBERS EXPOSED

7.1 INTRODUCTION

Nanotechnology is not a single technology. It is a multidisciplinary grouping of physical, chemical, biological engineering and electronic processes, materials etc in which the unifying characteristic is one of size. It spans well established industrial processes such as the manufacture of carbon black to high technology synthesis of quantum dots and wells. The area is expanding rapidly and there is large scale investment of Government funding. Organisations involved range from University departments, new spin-out companies and major multinational chemical and pharmaceutical groups. This diversity makes it difficult to estimate the numbers of individuals involved with any confidence. Certainly no single information source is available.

Our estimates are not based on an employment survey since this was not within our remit. Rather, they are best-estimates based on information available in the public domain coupled with assumptions about links between economic value and employment which have not been tested. As such they should be regarded as provisional "ball-park" estimates until such time as they are challenged or supported by an appropriately designed survey.

7.2 METHODOLOGY

The three main industrial activities in which exposure to deliberately manufactured nanoparticles can occur are:

(i) Nanotechnology sector, primarily research and development, including University departments and spin-out companies;

(ii) Existing ultrafine manufacture, manufacturing processes including carbon black and fumed silica; and

(iii) Powder handling processes including paints, pigments and cement manufacture.

In addition, exposure to nanoparticles can occur in other processes where the nanoparticles are by-products of the process. These include welding and refining.

Provided below is a summary of the methods used to identify the potential numbers of UK workers exposure to nanoparticles from these various industrial activities. Further information on the methods used is provided in Appendix 3.

To obtain an overview of potential numbers of individuals working in the nanotechnology sector and who may potentially be exposed to nanoparticles, both 'top – down' and 'bottom-up' methods were used.

The NanoInvestor News Company Database (http://www.nanoinvestornews.com/ncd.php) was searched which contains details of nanotechnology companies currently being tracked by NanoInvestorNews (part of NanoApex Corp., a media and market research company specializing in providing aggregated information, current news, and custom market research). This database provides a breakdown of nanotechnology companies by country and industrial sector, as well as brief overview of the type of work being currently undertaking. Whilst it is acknowledged that some companies involved in nanotechnology may not be included in this database, it was felt that it is at least one of the most comprehensive available.

It is currently estimated that there are 20,000 individuals working worldwide in nanotechnology today (NNI, 2004). Using the database, the number of UK nanotechnology companies was recorded and an estimate of the UK population employed in this sector was obtained by calculating the percentage of the worldwide market the UK represents and proportioning this to the NNI's (2004) estimate.

The numbers of individuals employed within nanoparticle manufacturing companies was estimated firstly by using the NanoInvestor News Company Database and other sources to identify companies involved in the manufacture of nanoparticles and assuming that 50 individuals per company are potentially exposed to nanaoparticles.

Web sites of the main University and research centres of nanotechnology expertise in the UK as listed on the ION web site (www.nano.org.uk) were searched to provide a summary of their main research activities and an estimate of the numbers of researchers involved.

The Institute of Nanotechnology has also recently published "Nanotechnology in the United Kingdom", which provides full information on all nanotechnology activity in the UK, including university research, government initiatives and policy, spin-out companies and large multinationals involved with nanotechnology. It is recommended that both this and Section 7 of this review should be referred to so to provide a more comprehensive review of the situation within the UK.

To obtain estimates of the numbers of individuals potentially exposed to nanoparticles from existing ultrafine manufacture and powder handling processes, two key sources of information was mainly used.

Wake's (2001) survey of ultrafine aerosols in the workplace identified key information on industries where ultrafine particles may be present, as well as some indication on the numbers of individuals involved within various companies. The Office of National Statistics (ONS) web site (www.statitsics.gov.uk) was also searched to obtain an indication of the numbers of individuals employed within these various industrial manufacturing and powder handling sectors. Estimates from other publicly available information were used where appropriate and are referred in Appendix 3.

Wake's (2001) survey and The Office of National Statistics web site were also the key sources of information used to estimate the numbers of UK employees potentially exposed to nanoparticle by-products from processes such as welding and refining.

7.3 LIMITATIONS IN ESTIMATING POTENTIAL NUMBERS EXPOSED

There are a number of limitations in estimating the potential numbers of people employed both in nanotechnology and also in processes where ultrafine aerosols may be present. For example:

- Nanotechnology is 'a multifaceted and malleable group of technologies' and it is difficult to associate it with specific areas of application.
- There is a growing ability to manipulate materials on the nanoscale, most of which will be in combination with non-nanotechnologies. Whilst most companies involved in nanotechnology will market themselves as such it is possible that some companies may not do so to the same extent as others and so might be overlooked.
- There are few readily available, comprehensive and up to date databases which contain summary company information.
- The numbers of companies involved in nanotechnology are increasing constantly; therefore any estimates will be soon redundant.

- Information on numbers of employees per company are not always available in the public domain
- Even when employee information is available, it is often unclear whether the figures cited are for total company employees or those specifically involved in manufacturing / research activities.
- It is not always obvious which country company manufacturing sites are located or indeed how many sites a company has.

Due to these and other limitations, the numbers cited in this section provide no more than a very broad estimate of the potential and predicted numbers of employees involved in nanotechnology and should not be taken as a definitive figure.

7.4 POTENTIAL UK EXPOSED POPULATION

Table 7.1 provides a summary of the number of individuals employed in the UK where occupational exposure to nanoparticles is possible. More detailed information on how these numbers were obtained is provided in Appendix 3 and is summarised below.

Considering firstly the UK university/research and new nanotechnology company group, our “top-down” estimate is based on the 2004 NNI estimate of 20,000 individuals working in nanotechnology. Approximately 22% of nanotechnology companies are currently based in the UK according to the NanoInvester news database. If it is assumed that the split in employment between the UK and the rest of the world is the same as the split in the number of companies this would indicate that up to 4,400 UK workers could be currently involved in this sector.

The NanoInvestor database also provides a breakdown of the main activities of nanotechnology companies. This indicates that from a list of 891 companies, 395 (44%) are involved in activities in which nanoparticle exposure could occur. If it is assumed that this distribution of activities is the same as in the UK, this would indicate the 1936 workers could potentially be exposed.

Our “bottom-up” estimate is based on the number of nanotechnology researchers in UK Universities and Government laboratories (Daresbury, Rutherford Appleton) identified primarily from website information (Appendix 3). On this basis we estimate that 2400 researchers are involved. If the activity distribution is assumed, this would indicate 1056 workers could be potentially exposed. In addition based on information from (two) companies we estimate that 858 workers are potentially exposed to nanoparticles. These estimates would imply that a total of 1914 workers.

Both of these estimates are similar and suggest that an estimate of 2000 for this area is reasonable. Both the top-down and bottom-up estimates are likely to over estimate the number of UK workers potentially exposed, since not everyone working in nanoparticle based companies will be exposed.

Based on the information available, a maximum of 500 workers are considered to potentially be exposed to nanoparticles through existing ultrafine, manufacturing processes. Most of these are involved in the manufacture of carbon black.

Nearly 102,000 individuals may potentially be exposed to fine powders through various powder handling processes, the majority of which being employed by the pharmaceutical industry. It is not possible to say what proportion of these may be exposed to nanoparticles although it must be expected that this will be small.

However it is the incidental production of nanoparticles through processes such as welding and refining where the majority of the UK exposed population are employed. We estimate that over a million workers are potentially exposed to nanoparticle by-products, mostly due to metal manufacturing processes, which is over eight times the number of workers estimated to be potentially exposed during the deliberate manufacture and handling of nanoparticles from new and existing processes.

Table 7.1 Summary details of exposure UK working population

	Number of individuals
Nanoparticle production, of which :	2,000
University and research centres	*1,100*
Nanoparticle manufacturing companies	*900*
Existing ultrafine manufacturing processes:	
Carbon Black manufacturing	*300*
Ultrafine titanium dioxide manufacturing	*0*
Fumed silica	*0*
Fumed alumina	*<120*
Precious metal blacks	*<50*
Powder handling processes:	
Pharmaceutical products (including manufacturing)	*56,800*
Carbon black	*2,000*
Ultrafine Titanium Dioxide	*50*
Cement	*4,000*
Paint etc	*28,000*
Pigments and dyes	*11,000*
Ultrafine by-products:	
Precious metal refining	*2,000*
Thermal spraying and coating	*25,000 (all metal treatment)*
Zinc refinery	*100*
Steel refinery	*28,000 (all steel and iron processes)*
Aluminium refinery	*12,000*
Nickel refinery	*4,000*
Metals casting	*30,000*
Metal grinding and welding	*391,000 (manufacture of fabricated metal products, except machinery and equipment)*
Manufacture of cutlery, hardware	*39,000*
Manufacture of other fabricated metal products	*82,000*
Manufacture of machinery and equipment not elsewhere classified	*366,000*
Soldering	*50,000*
Depleted uranium	*unknown*
Combustion sources	
e.g. vehicle exhausts and cooking processes	*Not estimated*

7.5 PREDICTING FUTURE NUMBERS OF EXPOSED WORKERS

Estimates of the size of the nanotechnology sector vary but it is probable that the rapid growth seen in the last few years will continue. The UK is a major player in this area as can be seen from the rapid increase in the numbers of publications relating to nanotechnology and the commitment by the UK Government through the DTI program of £100 million worth of Research Funds for the development of new materials products and processes.

In 2003, the Science & Innovation Minister, Lord Sainsbury announced a £90 million spend over the next six years to help industry harness commercial opportunity in nanotechnology. This money will be spent on collaborative research and a new network of micro and nanotechnology facilities to help businesses win a market share.

Laboratories around the world are working on new approaches and ways to scale up the technology to industrial levels. This can be seen by the construction of factories aimed at mass producing carbon nanotubes and fullerenes in Japan and now in the UK. It is hard to predict what products will move from the laboratory to the marketplace over time due to market forces and also the patchiness of the mechanisms to facilitate transfer of science from academia to industry. It is also difficult to predict what future applications of nanotechnology will be.

At the research and development level, it is very probable that this increased investment will result in an increase in those potentially exposed. In 2002, government spending on nanotechnology research and development was estimated to be £30 million per year (UK advisory group**,** 2002). The additional £90 million (plus at least £90 million matching funds from industry) over the next 6 years would result in an average annual spending of £60 million, effectively doubling the current research spend. It is not unreasonable to estimate that employment within this sector would also double over the next 6 years to deal with the corresponding increased workload.

It is reasonable to expect that the balance between numbers exposed in research and production and applications will shift, with greater emphasis and exposures being found during the secondary manufacturing of products. It has also been suggested that potential occupational and public exposure to manufactured nanoparticles will increase dramatically in the near future due to the ability of nanomaterial to improve the quality and performance of many consumer products the public employs daily as well as the development of medical therapies and tests which will use manufactured nanoparticles (Dreher, 2004).

The National Science Foundation has estimated that 2 million workers will be needed to support nanotechnology industries worldwide within 15 years (NNI, 2004). Based on the current distribution of activities we estimate that about one third of these will be involved in the manufacture and use of nanoparticles. However, as the industry grows, and the products become more commonplace it is probable that this proportion and therefore the total number of workers will increase beyond these numbers.

8. DISCUSSION

Nanotechnology

Nanotechnology is a broad interdisciplinary area of research, development and industrial activity which has been growing rapidly world wide for the past decade. The use of the term nanotechnology can be misleading since it is not a single technology or scientific discipline. Rather it is a multidisciplinary grouping of physical, chemical, biological, engineering, and electronic, processes, materials, applications and concepts in which the defining characteristic is one of size. The US National Nanotechnology Initiative (NNI) defines nanotechnology as;

- Research and technology development at the atomic, molecular or macro molecular levels in the length scale of 1-100 nm;
- Creating and using structures, devices and systems that have novel properties and functions because of their small size;
- The ability to control or manipulate on the atomic scale.

Growth predictions for this activity vary but there is wide agreement that the rapid expansion seen in the last few years will continue. Some estimates suggest that the size of the world market will increase by an order of magnitude in the next six years. The NNI initiative estimates that currently there are around 20,000 researchers working in the field of nanotechnology world-wide. The UK is a major player in this area as indicated by the rapid increase in the numbers of publications relating to nanotechnology and the commitment by the UK Government through the £100 million DTI program for the development of new nanomaterials products and processes (Section 1).

Nanoparticle production processes

There is no agreed definition of a nanoparticle but they are commonly considered to be particles having a dimension less the 100nm (Section 4.1). The development and application of nanoparticles represents a major portion of nanotechnology activity and the number of nanoparticle products continues to grow. The purpose of producing these new materials and products is that their behaviour is expected (and has been demonstrated) to be different in the nanometre scale than in the macroscale. Nanoparticles are produced using a wide range of synthesis methods by university and other research groups, small emerging companies, and by established major international organisations.

Particle morphology is a useful basis for categorising nanoparticles (Section 4.2). Nanotubes are a new form of carbon molecule with diameters which range from 2 – 20nm and lengths up to 1mm. Nanowires are particles with diameters up to 100nm also with large aspect ratios, which may be of metals, oxides or semiconductors. Nanodots are small nanoparticles usually semiconductors, with typical dimensions 1-10nm which exhibit quantum properties. The final category of “other” nanoparticles includes a wide range of primarily spherical or aggregated dendritic forms which can be synthesised from metals, oxides, ceramics and organics.

In this review, we considered the development and production of nanoparticle products from an occupational hygiene perspective, and have identified four main groups of methods by which nanoparticles may be produced (Section 5.1). These are:

1. Gas phase synthesis methods which generate particles by condensation and coagulation
2. Vapour deposition in which particles are grown on substrates and formers.
3. Colloidal methods, primarily wet chemistry precipitation processes.
4. Attrition methods which progressively reduce the particle size of coarse powders.

Although these processes are capable of producing materials with strikingly different properties from bulk forms of the same material, from an occupational hygiene perspective the processes themselves are not dissimilar to conventional well-established chemical and engineering processes.

Exposure

In principle, all of these production methods may give rise to exposure by inhalation, through the skin and by ingestion (Section 5.3).

Exposure by inhalation caused by direct leakage of nanoparticles into the workplace air during synthesis only seems possible in gas-phase processes. In vapour deposition, particle growth is on a substrate and in the colloidal and attrition methods particle formation is in the liquid phase', therefore aerosols will not be formed during synthesis. However, for all production methods, product recovery and subsequent processing are powder handling activities which, if sufficient energy is used, may result in the generation of respirable or inhalable concentrations of agglomerated nanoparticles. It is however very probable that these powder handling activities will not generate separated nanoparticles, due to the relatively high energies which would be necessary to break the (Van der Waals) forces which keep particles agglomerated. Even generation of larger agglomerations of nanoparticles as aerosols may be quite difficult.

All of the production processes described could potentially result in dermal exposure, particularly at the powder handling, packaging and bagging stages. Dermal exposure is likely to result in ingestion exposure from hand-to-mouth contact. It has been postulated that nanoparticle exposure to the skin can result in direct penetration through the skin. At least one pharmaceutical company is developing drug delivery systems based on topical application of lipid nanoparticles. It is therefore reasonable to conclude that nanoparticles depositing on the skin could potentially penetrate into the epidermis and possibly beyond. As far as the authors are aware toxicological effects arising from dermal exposure to nanoparticles, or from ingestion have not as yet been investigated or identified.

Based on current evidence, the most appropriate metric to use to assess exposure by inhalation to most nanoparticles is surface area (Section 4.3). This appears to fit best with current toxicological evidence and would deal directly with the issue of agglomeration. Ideally a personal sampler would be available which could assess this metric. There are however, no methods (personal or static) by which surface area may be measured directly in the workplace. Nor are there convenient or ready technologies which could easily be adapted to provide a solution to this issue. While a strong case may be made for using surface-area as a metric, this may not be universally so. For particles which could be considered to be fibres, such as carbon nanotubes, particle number may be more appropriate.

In any case, it is also necessary to consider characterising exposures against aerosol mass and number concentration until further information and improved methods are available (Section 4.4). For each of these exposure metrics, but particularly in the case of mass concentration, size-selective sampling will need to be employed to ensure only particles within the relevant size range are sampled.

For dermal exposure, measurements should also be biologically relevant. At this stage there is insufficient evidence to indicate whether mass, number or surface area is the most appropriate metric. Measurement approaches should ideally also consider the skin area exposed and the duration of exposure.

For ingestion exposure too, measurements should also be biologically relevant. There is insufficient evidence to indicate whether mass, number or surface area is the most appropriate metric.

Information about the exposure of workers to nanoparticles is extremely limited (Section 5.3). No information has been identified about workers exposures to nanoparticles in the university/research sector or in the new nanoparticle companies in the UK. Only one study, carried out in the US, has evaluated nanoparticle exposure (for carbon nanotubes). Only very limited information is available for existing chemical, pharmaceutical and refining companies. The limited information which is available uses either mass or number as an exposure metric, rather than surface area. The number based estimates are derived from static samplers rather than personal samplers. Information from other powder handling process indicates that exposures may be significant.

Control

Conventional control strategies and systems are available which may be used to control exposures in all of these synthesis processes (Chapter 6). Engineering controls should be able to be designed to provide sufficient levels of containment. Filtration systems including respiratory protective equipment should be effective providing that they are used and maintained correctly. However, it will be necessary though to use high-grade systems, such as those currently used for control of gases rather than particulates. While this suggests that it is quite feasible to control airborne exposures to nanoparticles through conventional control approaches, there is little or no available evidence in the literature to demonstrate that this has been achieved in current processes.

Until relatively recently, less emphasis has been placed on dermal exposure as a route of exposure. One consequence of this is that the effectiveness of control measures to prevent dermal exposures, are poorly understood and almost certainly not as effective as approaches to control exposure by inhalation. Given the relative difficulty in re-dispersing nanoparticles into an airborne state, it is possible that dermal exposure could be the principle route of exposure for many categories of nanoparticle. No published literature has been identified which has investigated the effectiveness of skin protective equipment (suits and gloves) against nanoparticles. It is recognised that skin protective equipment is limited in its effectiveness to prevent dermal exposure. It is unlikely that it will be more effective against nanoparticles than against larger particles. It is conceivable that for many current forms of skin protective equipment, nanoparticles could penetrate directly under certain conditions. Again, however, this has not been investigated or demonstrated.

For ingestion the issues are much the same as for dermal exposure. Exposure by ingestion is likely to arise where dermal exposure to the hands is present given that much of ingestion exposure is linked to hand to mouth contact. Consideration of exposures in relation to ingestion is at a very early stage. As with dermal exposure it is unlikely that any preventative methods for exposure by ingestion will be more effective for nanoparticles than for larger particles.

Risk Assessment

Proper assessment of the risks associated with exposure to nanoparticles requires understanding of the toxicological hazards associated with these materials and of the levels of exposure, expressed in an appropriate metric, which are likely to occur.

In the UK it is a requirement under COSHH that companies involved in the manufacture and use of chemicals carry out risk assessments. We have no reason to doubt that these are being done. Whether there is sufficient information available for these risk assessments to be carried out adequately in all cases is much less certain. Companies will use the best information available to them. This information needs to take account of the (potential) differences in the toxicological hazard and exposure characteristics between nanoparticle materials and bulk forms. Given that (based on this review) there are substantial gaps in the information available, it is difficult to see how these risk assessments can be adequate.

Regulatory risk assessment will in future be carried out under the REACH proposals. There are two aspects of these proposals which will result in nanoparticles not being assessed. As far as we are aware, the proposed implementation of REACH is concerned only with assessing different chemicals and takes no account of particle size. Therefore there will be no need to distinguish between, for example, nickel pellets and nickel nanoparticles. If there are differences between the toxicological and exposure characteristics of these two materials, these will not be accounted for.

The second aspect relates to the production mass limit. Currently under REACH, chemicals for which production in the EU is less than 100 tonnes, have a more limited evaluation procedure. Those for which volume is less than 1 ton do not require registration. Many of the nanoparticle materials will have low production volumes. As such under the current proposals they will not need to be assessed.

Employment

Approximately 2000 people are currently employed in the university/research sector and in new nanoparticle companies in activities in which they may potentially be exposed to nanoparticles in some form. Based on the information available, a maximum of 500 workers are considered to potentially exposed to nanoparticles through existing ultrafine, manufacturing processes. Most of these are involved in the manufacture of carbon black.

Nearly 102,000 individuals may potentially be exposed to fine powders through various powder handling processes, the majority of which being employed by the pharmaceutical industry. It is not possible to say what proportion of these may be exposed to nanoparticles.

However, is worth emphasising that most exposure to nanoparticles in the UK will be via the incidental production of nanoparticles through processes such as welding and refining. We estimate that over a million workers are potentially exposed to nanoparticle by-products, due to these processes, which is over eight times the number of workers estimated to be potentially exposed during the deliberate manufacture and handling of nanoparticles from new and existing processes.

The number of people in the university/research sectors, and in new nanoparticle companies may double over the next five years. The proportion of those involved in existing chemical and pharmaceutical companies and in other powder handling activities who are exposed to nanoparticles is likely to increase substantially as the use of nanoparticle materials increases.

Knowledge gaps

We have identified substantial knowledge gaps in relation to key issues. These are detailed below along with our view of how they may be addressed.

Gap 1: The nanoparticle nomenclature is not sufficiently well described or agreed

The establishment of an agreed and unified nomenclature is widely recognised as an important step towards development in any field of scientific endeavour. Currently there are no agreed definitions for nanoparticles, nanoparticle aerosols, or for the various types of nanoparticles which are produced. The first aspect relates to particle size. A definition of a size range for nanoparticles needs to take account of the distribution in sizes likely to be present, and to define the size interval in relation to the distribution. Secondly, it is necessary to consider whether the definition should be based on physical dimensions (e.g. length, diameter, surface area) or on some behavioural property such as diffusivity.

The definition of a nanoparticle aerosol needs to include some consideration of aggregation and agglomeration. For example, should an aerosol which is comprised of loosely bound agglomerates of primary nanoparticles, in which the agglomerates are a size or dimension larger than that normally regarded as a nanoparticle (e.g. 1000nm) be regarded as a nanoparticle aerosol?

Progress on nomenclature issues is usually best achieved based on consensus. The planned workshop on nanoparticle health risks (organised by HSE and NIOSH) to be held later this year will provide an ideal forum to discuss these issues.

Gap 2: There are no convenient methods by which exposures to nanoparticles in the workplace can be measured or assessed

There is a need for more research into the development of new improved methods, combinations and strategies to provide reliable assessments of exposure to nanoparticles and nanoparticle aerosols. For inhalation, the most appropriate metric for assessment of exposure to most nanoparticles is particle surface area. Currently there are no effective methods available by which particle surface area can be assessed in the workplace.

Failing the development of this measurement approach, two alternative strategies are available. One is to develop an appropriate exposure assessment approach which optimises information available from various sources. This could include using suitable instruments to measure mass and/or number, assessment of material bulk properties, identification of appropriate surrogate measures, use of appropriate models, and evaluating determinants of exposure in a structured way. Suitable combinations could include instrumentation to count and size particles, coupled with surface area measurements derived from BET measurements of bulk material. Surrogate measures could include measurements of chemical composition of the nanoparticle material or of trace elements or impurities. Various deterministic approaches are already in use to provide assessment of current and retrospective exposure levels in workplaces, (e.g. Cherrie, 1999) which offer the potential for use in the assessment of exposure to nanoparticles.

An alternative (or complementary) approach may be the development of biological assays which directly measure the toxic potential of collected samples. In principle, these could be based on *in-vitro* methods currently used in toxicological studies to assess inflammatory response. More research is required to develop and evaluate approaches of this type.

Development of appropriate methods to evaluate dermal and ingestion exposure is also necessary.

Gap 3: Insufficient information concerning nanoparticle exposure is available

Much more information is needed regarding the exposure of workers involved in the production of all of the various types of nanoparticles via all of the production processes. In the absence of suitable measurements systems coherent approaches as described above should be adopted. At this stage there is insufficient evidence to judge whether exposure to the various forms of nanoparticles is occurring at significant levels in nanoparticle production processes.

Gap 4: The effectiveness of control approaches has not been evaluated

Control methods are available which have the potential (at least for inhalation risks) to provide the basis for effective risk management. At this point, it is not easy to judge how effective control strategies need to be. For some specific nanoparticles it may be necessary to control to very low levels (e.g. ng m^{-3}). There is almost no information available in the public domain to demonstrate that effective control of exposure to nanoparticles has been achieved.

Better understanding is required relating to the effectiveness of control of nanoparticles. This will be better informed given the development of appropriate methods for assessment of exposure to nanoparticles and a better understanding on the levels of exposure which may be acceptable. This is true for both inhalation, dermal and ingestion risks.

Gap 5: Knowledge concerning nanoparticle risks is inadequate for risk assessments

Proper assessment of the risks associated with exposure to nanoparticles requires understanding of the toxicological hazard associated with these materials and of the levels of exposure, expressed in an appropriate metric, which are likely to occur. There is insufficient exposure information currently available to adequately assess the risks from exposure (by inhalation, dermal and ingestion) to nanoparticles in nanoparticle production processes. A toxicological review of these particles is out-with the scope of this review. However even a brief examination of these issues, strongly indicates a lack of information. Given the diversity of nanoparticle shape, size and function, risk assessments will by necessity be highly specific to particular groups or classes of nanoparticles. Risk assessment approaches will have to consider how best to use information which is currently available, and plan to collect new information. Methodological approaches are available which may be used in new studies. Appropriate and useful studies would include investigation of material properties (e.g. dustiness), exposure assessment and toxic potential within a structured risk assessment framework. These studies are unlikely to proceed without Governmental encouragement and support.

An effective strategy for storing and sharing this information is also necessary. Development of appropriate databases, and other information resources which can be used to collect and disseminate information on studies to investigate exposure or toxicological assessment of nanoparticles would be a key element in this.

Information resources of this type are already available to collect and disseminate information about exposure studies. One model is the HEROX database (www.herox.org) which contains information concerning exposure assessment studies for chemicals. This is a managed resource, with information concerning the studies being submitted by the researchers. This or other similar information resources could provide the basis for collection and storage of information about nanoparticle studies.

There is a strong case for placing more emphasis on issues of risk assessment and management than has been placed thus far. Development of new materials and products should not take place in the absence of consideration of the risks associated with their development, manufacture, use and ultimately disposal. Even though there are gaps in available approaches, a start can and should be made on the collection, dissemination and analysis of information relating to risks of these materials.

9. CONCLUSIONS

Based on our review of occupational hygiene aspects of nanoparticle production, we conclude that;

1. There are four main groups of nanoparticle production processes (gas-phase, vapour deposition, colloidal and attrition) all of which may potentially result in exposure by inhalation, dermal or ingestion routes.

2. From an occupational hygiene perspective, the processes are not dissimilar to existing chemical production processes

3. Only gas-phase processes have the potential to cause exposure to primary nanoparticles by inhalation during the synthesis stage. All processes may give rise to exposure (by inhalation, dermal and ingestion) to agglomerated nanoparticles during recovery, powder handling and product processing.

4. For exposure by inhalation, control approaches and methods are available which should be effective in nanoparticle processes.

5. For dermal or ingestion exposure, control methods based on personal protective equipment may not be as effective as they are in existing processes.

6. The most appropriate metric in most cases for assessment of inhalation exposure to nanoparticles is particle surface area. There are no effective methods currently available by which particle surface area can be assessed in the workplace.

7. Current knowledge is inadequate for risk assessment purposes.

8. No information has been identified about workers exposures to nanoparticles in the university/research sector or in the new nanoparticle companies in the UK. Only very limited information is available for existing chemical, pharmaceutical and refining companies. Information from other powder handling processes indicates that exposures may be significant.

9. Approximately 2000 people are currently employed in the university/research sectors and new nanoparticle companies in activities in which they may potentially be exposed to nanoparticles in some form. A maximum of 500 workers are considered to potentially be exposed to nanoparticles through existing ultrafine manufacturing processes, mostly the manufacture of carbon black. Around 100,000 individuals may potentially be exposed to fine powders through various powder handling processes, including the pharmaceutical industry. It is not possible to say what proportion of these may be exposed to nanoparticles. More that 1,000,000 workers in the UK may be exposed to nanoparticles via incidental production in processes such as welding and refining.

10. The number of people in the university/research sector, and in new nanoparticle companies may double over the next five years. The proportion of those involved in existing chemical and pharmaceutical companies and in other powder handling activities who are exposed to nanoparticles is likely to increase.

In summary, we conclude that there is little evidence to suggest that the exposure of workers arising from the production of nanoparticles has been adequately assessed.

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Various nanotechnology companies and University web sites were also consulted in this review and these are detailed elsewhere in the report.

APPENDIX 1: DATABASES AND SEARCH TERMS USED

A wide range of search terms were used both singly or in combination as necessary during the literature review. Table A1.1 provides details of the main keywords used for the various database searches.

Table A1.1 Databases and keywords used

Database	Keywords
Barbour Index	
	Nanoparticle(s)
	TiO2, Titanium Dioxide
	Foundry fume
	Ultrafine aerosols
	Ultrafine(s), ultra-fine, ultra fine
	Ultrafine particles
	Depleted Uranium
	High energy cutting
	Pigment manufacture
	Pharmaceutical industry
	Ultrafine carbon black
	Carbon black
	Carbon black exposure
	Pharmaceutical
	Pigments
	Uranium
	Thermal spray(s)
	Thermal coating
	Welding fume
	Galvanising
	Metal processes
	Zinc oxide fume
	Metal processing
	Fumed silica
	Aluminium smelting, aluminium smelter
	Steel smelting, steel smelter
	Iron smelting, iron smelter
CCOHS / Science Direct	
	Nanoparticles, nanomaterials, nanotubes, nanowires, nanocrystals, nanodots, quantum dots, nanotechnology and;
	synthesis, formation, review, inhalation exposure
	Titanium dioxide and;
	review, summary, ultrafine, particle size, manufacture, processes, production, exposure, ultrafine particles, occupational exposure, exposure levels, process
	Ultrafine particles and;
	processing, review
	Ultrafines and;
	review, exposure, inhalation, handling, production

	High energy cutting, high-energy and cutting
	Welding fume and; exposure levels, review
	Fumed silica and; inhalation, dermal, production, process, summary, review, exposure, ultrafine, aerosols, nanoparticles, ultrafine particles, controls, workers
	Fumed alumina; fumed alumina production
	Flame based powder generation
	Depleted Uranium and; exposure, review, uses, summary, ultrafine, particles, aerosols, dust
	Material handling and; aerosols, ultrafine, powders, exposure, processing.
	Pharmaceutical industry and; exposure, powder(s), particles, ultrafine, aerosols, inhalation, dermal, control, processes, occupational, review, workers, summary, manufacture, control measures, engineering controls, process control
	Powder handling
	Mechanical processes and; ultrafine particles, aerosols, particles, exposure, inhalation
	High speed grinding metal grinding, high speed grinding, metal grinding
	High energy drilling
	Aluminium smelting, smelter and exposure, ultrafine, aerosols, particles, inhalation exposure.
	Thermal silica and; ultrafine, exposure, aerosols, review, summary, process, production, controls, ultrafine particles, nanoparticles .
	Pyrogenic silica and; process, particles, aerosols, workers, ultrafine, exposure, production
	Nanoparticles and; inhalation, dermal, exposure, dermal exposure, inhalation exposure, occupation, airborne, handling
	Nanometerials and; inhalation, exposure, dermal, occupation, airborne, handling
	Nanotechnology and; exposure, inhalation, dermal and aerosols.
	Pyrogenic silica and; process, particles, aerosols, workers, ultrafine, exposure, production

APPENDIX 2: PROBABLE LEVELS OF EXPOSURE IN EXISTING INDUSTRIES

A2.1 Introduction

The main existing industrial activities in which exposure to deliberately manufactured nanoparticles could occur are manufacturing processes including carbon black, fumed alumina and precious metal blacks and various powder handling processes such as those in the pharmaceutical and titanium dioxide industries. In addition, exposure to nanoparticles can occur in other processes where nanoparticles are produced as unwanted by-products such as during welding soldering and foundry activities. Nanoparticles can be present in the atmosphere from vehicle exhaust emissions and a wide variety of physical, chemical and biological processes however exposure from these sources, both occupational and otherwise is not discussed. Wake (2001) carried out a review of industries based in the UK to determine if they produce, handle or generate ultrafine particles / powders and if so, identify which processes give rise to the generation of such aerosols and obtain relevant exposure measurements. This work is summarized within the following sections along with key process details and information concerning routes of exposure and any appropriate supplementary information from additional published studies identified. It was noted during this review that very few papers discussed these industrial processes in relation to occupational exposure to ultrafine aerosols, instead focusing on total exposure to particulates and other hazardous substances. It was also noted that Riediger and Moehlmann (2001) undertook a study to measure ultrafine aerosols in selected industrial workplaces and the efficiency of different respiratory particle filters against ultrafine particles. This paper is in German and a translated copy was not obtained during the timescale of this study

A2.2 Fumed silica (silicon dioxide)

Pratsinis (1998) discusses the synthesis of fumed silica ceramic powders using flame aerosol rectors. Fumed silica is one of the major chemical products of industrial importance and it is produced at about 100,000 tons /year in 1991 worldwide. Fumed silica is used in optical fibres, filler in silicone rubber, thickening, antisettling and reinforcing agents, catalyst carriers, polishing material in microelectronics to name but a few. According to this process, $SiCl_4$ (silicon tetrachloride) is continually vaporized, mixed with gases and fed to the burner where silica aerosol is formed. The silica is separated from the hydrogen chloride (HCl)-containing gases by cyclone separators or filters and further purified from absorbed HCl on its large surface area by steam and air treatment in fluidised beds. Depending on the process conditions, the specific surface area of fumed silica is $50\sim380m^2/g$, made of aggregates of amorphous spherical primary particles up to a few nanometers in diameter each. Studies concerning the synthesis of fumed silica using various types of flames and conditions are reviewed by Pratsinis (1998). For example increasing flame temperature was found to enhance homogenous nucleation, leading to smaller particles in higher numbers. Fumed silica particles form at temperatures around their melting or softening temperature and as they aggregate they form short, chain-like structures.

A2.3 Alumina powder

Alumina powder can also be produced using flame aerosol reactors and is used for production of integrated circuit substrates, high pressure sodium-vapour lamps, catalysts supports, cutting tools, heat and wear-resistant materials and as shielding material in radioactive systems. It is also finding new applications in the preparation of high temperature filters, coatings and membrane supports suitable for liquid or gas separations (Pratsinis, 1996).

There are basically five stages in the alumina refining process:

- Crushing – Any ore handled and crushed in either ball or rod mills.
- Digestion – Slurry is formed from the ground and blended bauxite ore and caustic acid is added, digesting the slurry to form ‘green’ liquor. This is carried out at high temperatures. Caustic mist is the main exposure here.
- Clarification – This is a four stage process which is basically the purification of the liquor where it is washed and also cooled. Caustic mist is the main exposure here.
- Precipitation – Hydrated alumina is cooled and precipitated.
- Calcination – This involves the removal of water from the alumina hydrate. The hydrated alumina is heated to 1000^0C in rotary kilns or calciners (Benke *et al*; 1998).

Particle sizes

Alumina powder is said to have a median mass diameter of 100µm and the range of respirable faction of the powder being less than 2% (Soyseth *et al*; 1997).

Sources of exposure and typical levels

Exposure to alumina dust can occur during the calcinations process if effective dust controls are not in place. In Benke *et al* (1998) review of exposures in the aluminium and primary aluminium industry, Tomaszewski *et al* (1983) reported that most of the alumina dust exposures at a shipping port were found to be of the respirable size.

A2.4 Carbon black industry

Production

Carbon black is a powdered form of elemental carbon manufactured by the controlled vapour-phase pyrolysis of hydrocarbons. Worldwide production of carbon black was approximately 6 million tonnes in 1993 (IARC, 1996). Carbon blacks are classified according to the production process used. The main processes are furnace black and thermal black.

Furnace Black – this is the predominant manufacturing process, accounting for more than 98% of worldwide production. An aromatic liquid feedstock, derived from coal or petroleum, is steam atomised into a flame at between 1300 and 1850°C in a refractory-lined or water-cooled reactor (Rivin, 1986). Carbon black formed in the flame zone passes through the furnace section at high velocity, after which the carbon laden gas is cooled to about 300°C by water sprays and then filtered through coated glass fibre or Teflon fabric filter bags to remove and collect the very fine carbon black particles (“fluffy” black).

Thermal Black - a chamber filled with chequered brickwork is heated to about 1300°C and the hydrocarbon feedstock (gas or vaporised oil) is then injected (Gardiner *et al;* 1992). Contact with the hot bricks causes the feedstock to crack, producing carbon suspended in an off-gas composed of >85% hydrogen plus methane and heavier hydrocarbons. After cooling with a water spray, the carbon black is removed by cyclone separators followed by bag filters or water scrubbers. Two reactors are operated in tandem; one being heated by combustion of recycled gas in air while the other is producing carbon black. This process accounts for approximately 2% of word-wide production.

In Great Britain, only two factories manufacture carbon black, one of which uses the furnace black process alone, whilst the other uses both the furnace and thermal black processes. The total annual production of carbon black in Great Britain is approximately 190,000 tonnes per year. Approximately 300 people are employed in the production of carbon black in Great Britain.

Processing

Once separated from the gases, carbon black is collected, pulverised and then dried. Wake (2001) observed that 'fluffy' black was passed via bag filters into storage hoppers for subsequent bagging or pelletised by the addition of water and a binder and then dried. Some regrinding may also be undertaken. A high percentage of the carbon black manufactured is pelletised before packing, to simplify transport and use.

Potential for exposure and controls typically used

In the fine carbon black factory visited by Wake (2001), most of plant process was observed to be enclosed and packaging operations and plant maintenance were deemed to have the greatest potential for operator exposure. The packaging of the material was either carried out as direct loading into container lorries, which is fully enclosed, or poured into large bags at several manned loading stations. Powered respirators were also observed to be worn during bagging and maintenance operations.

Particle sizes

Carbon black is an amorphous carbon composed of particles and fused aggregates. Particle size, surface area, average aggregate mass distributions, morphology or structure and chemical composition differentiate the various grades of carbon black. Primary particles fuse in the manufacturing process to form aggregates. Aggregates typically cluster into agglomerates. Commercial carbon blacks are highly agglomerated with 10 to 1,000 aggregates per agglomerate. In the workplace agglomerates of carbon black predominate, and airborne particle sizes usually exceed 2µm. Surface areas of agglomerates range from 5-200m^2/g. Thermal blacks, because of their large primary particle size and low degree of agglomeration, usually have surface areas at the low end of the range, 5-15m^2/g (IARC, 1996). The physical and chemical properties of the various types of carbon black are listed in Table A2.2.

Table A2.2: Typical Ranges and Properties for Four Types of Carbon Black (IARC, 1996)

Properties	**Acetylene black**	**Furnace black**	**Lamp black**	**Thermal black**
Primary particle size (nm)	35-50	17-70	50-100	150-500
Average aggregate size (nm)	NR	80-500	NR	300-810
Surface area (m^2/g)	60-70	29-200	17-25	6-15

NR: Not reported

The fundamental physical entity of carbon black is an aggregate (typically 50-200nm), which is a permanent rigid structure composed of spheres of carbon which have grown together during carbon black formation. These spheres are referred to in the industry as primary particles, but by the time the carbon black leaves the reactor they have no independent existence. The primary particle size is important in describing the surface area of the carbon black, but it is the aggregate dimension that describes the size of the smallest physical entity; i.e. the "particle size" of a given carbon black has no relevance to the material in the workplace air waiting to be inhaled.

Inhalation exposure

Kuhlbusch *et al* (2001) showed that airborne particles found in carbon black manufacturing plants are not individual aggregates, but agglomerates of many carbon black aggregates. They also concluded that no ultrafine (<100nm) and very few fine (<1000nm) particles were to be found at carbon black manufacturing sites. In Wake's (2001) measurements were made near the bagging of fluffy and pelletised carbon, the loading bay area (not during loading though) and in the general body of the factory where there was no activity. Workplace size distributions with high median diameters were seen in some measurements but these were very transient, usually occurring over 1or 2 minutes during bagging of fluffy and pelletised carbon. The size of the peaks in these distributions was found to be consistent with the size of the primary particles of the material involved. It was thought that agglomeration was taking place very rapidly because the peaks were transient and also not observed in size distributions measured in any other areas of the plant. Extremely high ultrafine particle counts were recorded outside the factory in the loading bay area and this was thought to be due to diesel exhaust fumes from lorries and also the close proximity of thefactory to a large oil refinery.

Table A2.3 provides an overview of the exposure levels found in the carbon black manufacturing and user industries. This data obtained from WATCH's carbon black review includes data from a variety of sources and includes only that which is less than 10 years old (IARC, 1996). Whilst the exposure data in the manufacturing industry can be assumed to be carbon black, the data from the users, in the main, relate to general (non-specific) dust, rather than carbon black per se. Data has been selected from areas in industry where exposure to carbon black is likely to occur.

Table A2.3: Overview of carbon black exposure levels

Industry	**Dust type**	**No of samples**	**Range of results mg m^{-3}**	**Range of means mg m^{-3}**	**Remarks**
Manufacture: Gardiner *et al* (1992 & 1996) van Tongeren *et al* (2000a & 2000b)	CB – inhalable	1126	<LOD – 37	0.3 – 10.4	UK data only
Gardiner *et al;* 1992 & 1996 van Tongeren *et al* (2000a & 2000b)	CB – respirable	1096	<LOD – 7	0.1 – 1.5	
Users					
HSE (rubber): NEDB	General – inhalable	20	0.9 – 57	1.1-47.9	Rubber UK only
HSE (other): Unpublished report	General – inhalable CB – inhalable	60	0.01 – 4 0.001 - 0.6	-	Toner manufacture
Published (rubber): Meijer *et al* (1998) Dost *et al* (2000) Vermeulen, personal communication	General – inhalable	198	0 – 30	1.1-9.4	Rubber
Published: Canham (1996)	General	Not known	0.03 – 1	-	Toner cartridge recycling
Industry (various)	CB – inhalable	38	<LOD – 9.5	0.1-7.0	
Industry (various)	General – inhalable	216	<LOD - 23	0.0-11.7	

Interpretation of most of the exposure data from the user industries is difficult. First of all, most measurements related to exposure are to inhalable dust, not just carbon black. In addition, it was often unclear if these measurements were representative of general exposure conditions or if they were taken during specially selected activities or worst-case scenarios.

A2.5 Nickel powder

Production

Wake (2001) visited a nickel refinery which used the Mond process to extract nickel from a matte consisting of copper-nickel sulphates. Matte is roasted to obtain oxides, copper is leached out and nickel oxide is reduced to nickel with hydrogen. Finally the nickel combines with carbon monoxide which decomposes by heating.

Particle sizes

The process of producing fine nickel powder makes it possible to have very precise control over both the size and morphology of the products, with various grades of powders ranging in size from 100 nanometres to 12 microns in diameter (Wake, 2001).

Potential for exposure and controls typically used

In the factory visited by Wake (2001), the whole process, up to stage where powder is removed, was enclosed due to concern of gas exposure and there is therefore little likelihood of operator exposure to dust. After collection, the powder is pressure fed into hoppers and then into integrated bulk containers. In the case of very fine powders, these are manually re-fed into the transport system to aid the transport process. No special containment was present in the packaging area other than natural ventilation. Workers were observed to wear powered respirators.

Particle sizes and workplace exposure

In Wake’s (2001) study, the finest grades of powder were being produced and handled and only the packaging areas were monitored. Measured size distributions median diameters of the ambient aerosols were very similar to those in the workplace indicating very little contribution from the latter (as is also indicated by similarly low workplace and ambient counts). This could indicate that the nickel powder is agglomerated throughout all the stages of its handling even after aerosilation. Wake (2001) does also state that even though individual ultrafine particles or agglomerates of ultrafines still in the ultrafine region were not detected in the air at the factory this does not mean that they can be discounted. This is especially true if the individual ultrafine particles have a large surface area (as do the nickel particles) and if they are present in the air as agglomerates, which takes them outside the ultrafine size range. During this visit the APS was not available to substantiate this. Where fundamental or primary particles are ultrafine, it is very likely that the powders will be agglomerated and that the resulting agglomerated particles may not be ultrafine. Measurements with the Scanning Mobility Particle Sizer (SMPS) of the workplace aerosols were complicated by the presence of diesel powered fork lift trucks in the loading bay area however the values in Table 5.7 are for measurements made when no fork lift trucks were operating in the area.

A2.6 Precious metal black

Production

The production of high specific surface area precious metal blacks was observed by Wake (2001). At the plant the metal blacks were produced in the form of suspensions or slurries and production was carried out in enclosed reaction vats in a small scale. These are washed to remove solids, dried in an oven and then sieved either by hand or using a mechanical shaker in a fume cupboard.

Potential for exposure and controls typically used

Potential sources of exposure to ultrafines were deemed to be when the product is removed from the ovens, the sieving operation, cleaning the sieves and removal of the dust from the drains and filters (Wake, 2001).

Particle sizes and workplace exposure

At the time of the visit, the finest grade platinum black was being produced and monitoring was undertaken during the sieving operation. Wake (2001) found that there was no increase in the number of ultrafines above ambient levels even when potentially dusty operations such as sieving were being carried out. The high ambient ultrafine counts recorded were thought to be due to exhaust emission for diesel powered fork lift trucks operating frequently outside the factory.

A2.7 Titanium Dioxide (TiO_2)

Production

Titanium dioxide is widely used in a variety of products. Ultrafine TiO_2 powders are used in cosmetics, pigments, toner, coating material etc. Two main processes are used for making TiO_2 pigments:

> **Sulphate process:** This is a batch process in which rutile or anatase TiO_2 is produced by digesting ilmenite or titanium slag with sulphuric acid and settling, filtration, concentration, collection and washing processes. Slag may be produced by smelting ilmenite in an electric furnace. The product is eventually ground and filtered, dried and pulverised.
>
> **Chloride process:** This is a continuous process where ore is ground and mixed with coke in a fluidised or static bed reactor and chlorinated at high temperatures. Fine grained oxides produced are sometimes calcined to remove residues.

Ultrafine TiO_2, comprising agglomerates of needle like primary particles approximately 20 by 100 nanometres in size, (although the particle size range depends on the process conditions) was readily available worldwide, mainly from Japan (Wake, 2001). Preparation of ultrafine TiO_2 by gas phase reaction is becoming an important technology.

Nearly 3 million tons of submicron TiO_2 is produced annually worldwide and demand is expected to surpass supply by the year 2000. Half of this is made in flame reactors by the chloride process.

Processing

In Wakes (2001) study, ultrafine TiO_2 was supplied and processed at a plant manufacturing cosmetics and lotions. Processing of the powder involved the following:

- Powder was oven dried to remove excess moisture and then mixed with water or oil,
- Resulting suspension repeatedly ground in a bead mill,
- Suspension packaged in intermediate bulk containers (IBCs) for transportation,
- Large unsealed IBCs are also used to transfer dried TiO_2 to the mixing and grinding plant.

Potential for exposure and controls typically used

Heaviest exposures (to TiO_2 not ultrafine specifically) are thought to occur in the milling and packing areas (which are generally located adjacent to each other). For workers in these jobs, heavy exposures can occur on a daily basis. Lower but consistent exposures may occur for treatment operators involved in the addition of special coatings and treatments to TiO_2 pigments before milling and packing. Maintenance workers may be exposed to short periods of heavy TiO_2 exposure. General labourers and laboratory staff may also have minimal exposure (Fryzek *et al;* 2003). (Exposures were for total dust and did not look at various sizes)

In ultrafine TiO_2 processing, most of the plant was enclosed however there are areas where the potential for aerosolisation was high such as around the large IBCs which contained the supplied raw TiO_2 (Wake, 2001). Dried TiO_2 was introduced to the mixing and grinding plant under vacuum.

Particle sizes and workplace exposure

Typical median particle sizes for anatase and rutile pigments range from 0.2 -0.3µm (LeSota, 1978; Schurr, 1981). A quick survey of TiO_2 nanoparticles being sold in the US for use in cosmetics shows that their size is not exactly precision-tuned, with the particles falling within a range between about 20 and 50 nanometres (ETC group, 2003).

Although it is apparent that occupational exposure to TiO_2 is extensive, there are few data on levels and sources of exposure (Santodonta *et al;* 1985) and the data available in the literature are reported as total dust or nuisance dust and not as TiO_2 and certainly no information on ultrafine exposure is given. Concentrations ranged from 10 to 400 mg m^{-3} during the grinding of TiO_2 pigment but documentation of these levels was not provided (Elo *et al;* 1972). Long term exposures to TiO_2 dust in a titanium pigment production factory occasionally exceeded 10 mg m^{-3} and exposure greater than 10mg m^{-3} were common during the repair of production machinery (Rode *et al;* 1981).

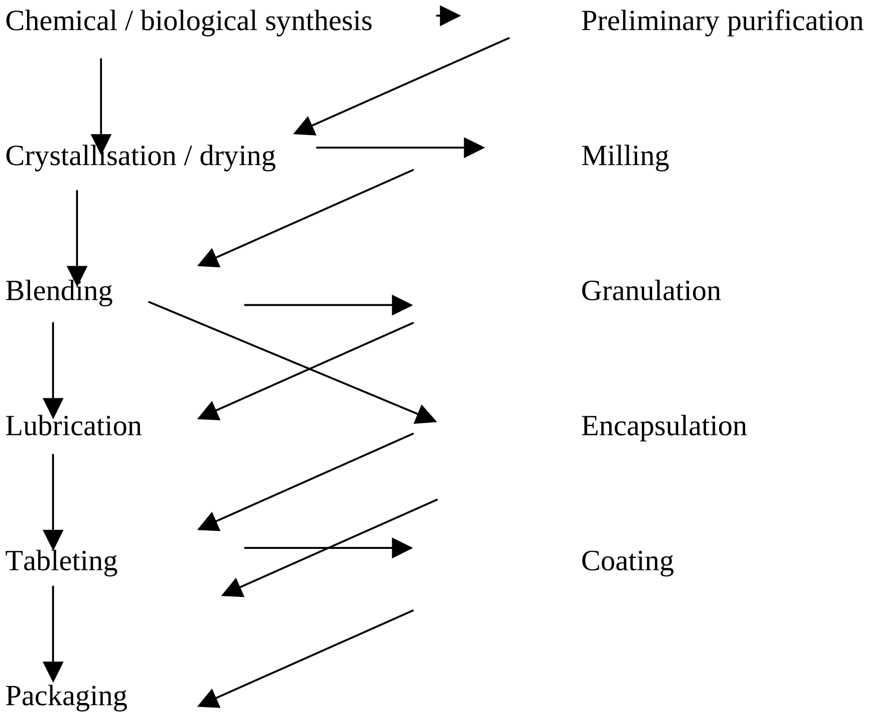
With regards to levels of ultrafine particle exposure, Wake (2001) undertook measurements during the transference of powder into an emulsifier and also during the transference of powder between large storage vessels. The conclusions Wake reached concerning the conditions at the precious metal black factory were said to be the same for the TiO_2 factory, with the highest levels being observed outside the factory near the road. The levels inside the factory were much lower probably as a result of very efficient recirculating local extract ventilation LEV.

A2.8 Pharmaceutical Industry

Processes

The production of pharmaceutical drugs is basically a two stage process. During primary manufacturing of the active pharmaceutical ingredient, operations such as drum charging, unloading reaction vessels, sampling, drying and milling occur. Once the dosage formulation is designed, companies develop batch manufacturing processes to make large numbers of units. Due to the complexity of dosage forms produced, formulation of the drug product (secondary manufacture) can involve a variety of operations including sieving, compressing, granulation, filling and packing (Binks, 2003). Figure A2.1 illustrates a sequence of operations which are representative of the operations involved in making tablets and capsules (which compromise roughly 80% of all pharmaceutical products for US consumption). This manufacturing process is largely powder technology in a variety of guises, with the entire sequence of operations being devoted to making particles, modifying their properties and turning them into structural products. Whilst Figure A2.1 is appropriate to the manufacture of tablets and capsules, powder technology operations also extremely prevalent in other types of pharmaceutical products including aerosols, injectable products, suspensions and topical creams.

Figure A2.1: Tablet and capsule manufacturing operations (Muzzio *et al;* 2002)



The list of classic particle technology operations relevant to Figure A2.1 include: Slurry reactions; Powder suspension and dissolution; Batch crystallization / precipitation; Milling; Filter drying; Fluidized bed drying; Spray drying; Particle coating; Wet and melt granulations; Dry blending; High shear de-agglomeration; Powder and granule conveying; Roller compaction; Tableting; Capsule filling and Coating (Muzzio *et al*; 2002).

Potential sources of exposure and typical exposure levels

Table A2.4 shows some typical potential dust exposures by task however it is recognised that for each of these activities, improved work practices and modification of exhaust ventilation can significantly reduce airborne dust levels.

Table A2.4: Typical potential dust levels by task (Naumann and Sargent, 1997)

Activity	**Conc. mg m^{-3}**
Dumping from drums	0.9
Dumping from bags	1.2
Scooping out of drums	0.8
Filling drums from blender	0.6
Bin transfers	0.2
Digging centrifuge	0.3
Milling	2.3
Tray dumping	2.7
Film coating	0.1
Sieving	0.8
Granulating	0.9
Compressing	0.08
Packaging	0.01
Sampling	0.01
Encapsulating	0.05

However, as can be seen from Table A2.4, operations such as milling, tray dumping and dumping from bags have the greatest potential for dust exposure whilst activities such as packaging, sampling and encapsulating would appear to be more controlled. Indeed Binks (2003) noted that primary manufacturing operations can generate short-term personal exposures in excess of 10 mg m^{-3} in the absence of appropriate controls and that dispensing of the active drug for formulations produces the greatest potential for high exposures. Burling and Shah (1997) suggest that for tableting and capsule operations, mixing, blending, granulation, compression, coating, capsule filling and packaging have the greatest potential for exposure which weighing, mixing, sterile mixing and packaging are also the most problematic operations in producing parenteral preparations.

Guest and Newton (1997) summarises the types of control measures commonly used for primary and secondary manufacturing operations. Primary operations typically range from LEV and barrier technology. Traditional controls and PPE may provide adequate protection for intermediates with minimal bio-activity, with complete containment maybe necessary for late-stage intermediates and final product. They also state that product transfers can sometimes be done without ever exposing the product to the outside environment. Secondary operations are usually batch and whilst ideally engineering controls alone would be used, appropriate technology may not always be available for all process operations. PPE is therefore sometime necessary to control residual unacceptable exposures.

A2.9 Ultrafine by-products

A2.9.1 Thermal spraying and coating

Process

A powder or wire is partially melted and then deposited onto a surface to give a thin metallic layer. Gas or plasma flames were used with the powders.

Routes of exposure

Wake (2001) observed the use of ventilated (flame spraying either hand held or automated) and enclosed (automated plasma spraying) spray booths. Details of the booths specifications are given in his report. The operator frequently entered the booth during the coating operation, initially to change the type of powder being used, make adjustments to position of work-piece and to take measurements of coating thickness. During these times the plasma torch was switched off. Operator was reported to only be exposed to powders when he was pouring them into the plasma gun.

Particles sizes

In tbe powder coating process, the particles were generally in the region of between 1 to 5 microns in diameter.

Exposure

Measurements were undertaken during plasma coating operations, hand held flame spraying and hand held wire spraying. The size distribution diameters in the workplace during this process were found to be higher than the ambient; which is consistent with other processes such as welding, which involve heat. Not shown in table 5.7, is that the SMPS particle number counts associated with the observed size distributions were also very high. A total number concentration of approximately 900,000 particles per cubic centimetre of air was observed when the size distribution medium diameter attained 587 nanometres during the wire spraying operation. The reason why the Portacount, which was sampling simultaneously, did not record similar levels is not known but it could be possibly explained by the position of this instrument being upstream to the wire spraying operation.

In Sioutas (1999) study aimed at characterizing fine particles (e.g. smaller than about 3μm) in an automotive plant, the average 24-hour mass concentrations of particles smaller than 3.2μm in aerodynamic diameter was 112.7 μg m^{-3} for heat treatment processes with the mass median diameter being approximately 0.5μm.

A2.9.2 Metal processing and refining plant – zinc refinery

Process

Wake (2001) surveyed a zinc refinery. The processes they were mainly involved with included:

- Handling and storage of zinc ore
- Proportioning of ore – mixing it with other ingredients
- Heating or sintering proportioned material to obtain unrefined metal
- Metal refined and purified through several processes involving heating
- Reheating and purification of zinc blocks after dross removal

Controls

Workers in all parts of the plant wore either powdered respirators or disposable filtering face masks (Wake, 2001).

Exposure

Most of the fume is thought to be produced near to the refining furnaces and purification areas. Sinter houses, proportioning area and the ore store were also thought to be areas where exposure may occur (Wake, 2001).

Exposure levels

At the time of the visit, the furnaces in which the raw metal was refined was not in operation. Levels of aerosol were high on the top floor of the factory but the workers did not often go there. Slight variation in the workplace median diameters of the size distributions of the aerosols were observed in different parts of the plant and the reason for this could be due to some of the processes producing a mixture of both fume and dust -the median diameters being lower and the particle counts being higher when this was the case. The size distribution median diameter of the aerosol outside the refinery was larger than that measured inside during any of the processes and this was thought to be due to re-suspension of dust from the ground (Wake, 2001).

In Sioutas (1999) study aimed at characterizing fine particles (e.g. smaller than about 3μm) in an automotive plant, the average 24-hour mass concentrations of particles smaller than 3.2μm in aerodynamic diameter was 201.7 μg m^{-3} for mild steel with the mass median diameter for machining processes being approximately 0.6μm. In recent studies in automotive operations, (Woskie *et al;* 1994a) found that, depending on the machining and metal-working fluid type, the mass median diameter of the aerosols ranged from 3.6-6μm. In another study by Woskie *et al;* (1994b) one of the main findings was that the greatest aerosol concentrations were produced by high-speed operations using soluble metal-working fluid in a high solute / oil content. Chan *et al*; (1990) found that fine particles (0.1-1μm range) were produced from actual, high-shear machining operations and that airborne mass concentrations were unaffected by variations in temperature and relative humidity but the size distributions depended greatly on the nature of the operation and type of machining fluid.

A2.9.3 Steel foundry

Process

The founding process is simple and highly adaptable. It consists of forming a hollow space, the mould, in the shape of the desired artefact in some refactory material. Molten metal is poured into the space and the metal is allowed to solidify (Smillie *et al*; 1994). Smillie *et al (*1994) provides an overview of the various operations found in a foundry. These include pattern making, core and mould making, metal melting, pouring and cooling, knock out, sand return and reclamation, cast cleaning and fettling and dressing.

Potential sources of exposure and controls

In the steel foundry monitored by Wake (2001), ultrafine aerosols were considered to be generated in three areas. These were:

- **Furnace area** – (two electric arc furnaces and several crucibles)
  The metal is melted in a furnace. Steel can be melted in direct or indirect electric arc or induction furnaces. The types of contaminants arising depend on the type and composition of metal being melted and any pre-treatments undertaken (Smillie *et al*; 1994).

- **Moulding area** – (casting and ‘knocking out’ areas).
  The pouring of molten metal into the mould gives rise to organic substances, smoke and gases and a lesser extent metallurgical fume. In mechanised foundries where the moulds are carried on conveyors, a central pouring location is usual. The rate of emission of contaminants decreases with time but in foundries producing a number of large castings per day, the generation of airborne contaminants may be continuous due to the time taken to cool sufficiently for knocking out. Knock out is the process where the moulding box, casting and core sand are separated and dust and gases can be evolved in large quantities (Smillie *et al*; 1994).

- **Fettling area** – (fettling and welding booths present here)
  This is where castings are treated further to remove excess metal. The practice is similar in iron and steel foundries except that in steel foundries higher temperatures may be used. The methods include air-carbon arc torches and oxy-gas cutting and washing tools. These hot cutting operations can be sources of fumes similar to welding fume. Various grinders and other tools may be used to remove excess metal and defects (Smillie *et al*; 1994).

In Wake (2001) visit, the area was ventilated by two axial fans mounted in the roof at each end of the factory and also naturally ventilated through holes in the brickwork in roof area and doors being left open. The furnace area was visibly the region where most fume was being generated, especially when the doors to the furnaces were opened.

Exposure levels

Measurements could only be made in the fettling and moulding areas (Wake, 2001). High levels of ultrafine aerosols were always evident in all areas of the factory. The high levels outside were attributed to the contribution of the ultrafines in the foundry air, which was leaving the factory close to where the outside measurements were made. The size distribution median diameters of the observed aerosol were slightly higher than ambient but were significantly higher during periods when it was known that MIG welding operations were being carried out. Other work (Wake and Brown, 1998) when measurements of ultrafine particles at the same foundry were made over a period of 3 days, showed that whilst levels were always high they could vary considerably during the day and that exhaust particles from a major motorway near by could be significantly contributing to these fluctuating levels (Wake, 2001).

Smillie *et al* (1994) summaries dust measurements data from UK foundries however exposure to ultrafine aerosols is not discussed. A study by Thorton and Lambert (1968) examined respirable dust concentrations in the UK steel casting industry and reported that mean concentrations were highest for arc gouging (13.5 mg m^{-3}), burning (4.6 mg m^{-3})and fettling areas (1.3-2.4 mg m^{-3}) areas. Later work by Stott (1978) found that air carbon arc, welding and grinding produced the highest levels of dust / fume concentration.

A2.9.4 Aluminium smelter

Process

The Hall-Heroult process is the major industrial process for the production of aluminium. Aluminium is produced by the electrolytic reduction of alumina dissolved in a carbon lined bath of molten cryolite. The Hall-Heroult process is the major industrial process for the production of aluminium. Aluminium fluoride, AlF_3 is also present to reduce the melting point of the cryolite. The mixture is electrolysed and liquid aluminium is produced at the cathode. The carbon anode is oxidised and bubbles away as carbon dioxide.

There are two types of processes – prebaked and Soderberg. Soderberg uses liquid anodes, poured continuously on top of the hot electrolytic bath and accounts for about half the worlds smelting capacity and there is currently at least one plant in the UK. Production is continuous, with aluminium being periodically taped off. Prebake technology is named after its anodes, which are baked in very large gas-fired ovens at high temperature before being lowered by various heavy industrial lifting systems into the electrolytic solution. There are also secondary smelters where aluminium is produced from old scrap. Healy *et al* (2001) carried out an exposure survey at 7 UK secondary aluminium smelters though as with other studies, did not investigate ultrafine particle exposure, focusing instead on inhalable dust and other airborne pollutants.

Aerosol exposure

The most significant operations generating exposure are as follows:

- Charging furnaces.
- Scraping walls of induction furnaces prior to transferring to holding furnaces or casting.
- Skimming dross from surface of molten aluminium prior to transferring or casting.
- Slagging out certain type of furnaces after molten aluminium has been transferred or cast.
- Possible addition of sodium.
- Blowing nitrogen through molten alloys (Healy *et al*; 2001).

Although exposure to ultrafine aerosols was not assessed, personal inhalable dust was assessed for various furnaces and processes by Healy *et al* (2001). The mean results (μg/m^3) were as follows:

- Rotary furnace – 3700
- Sloping hearth – 2100
- Induction – 2200
- Reverberatory / holding – 2400
- Casting - 800

Exposures are usually short and high, interspersed with long periods of low exposure.

A2.9.5 Welding

Process

There are more than 80 different types of welding processes and each process uses a wide variety of alloys and fluxing agents. Welding operations product gaseous and aerosol by-products composed of an array of metals, metal oxides and other chemical species. Welding processes are known to generate aerosols with a significant fraction in the nanometer size range.

Wake (2001) measured the aerosols produced during metal inert gas (MIG) and mixed metal arc (MMA) welding of steel plates undertaken in a laboratory which was naturally ventilated.

Particle sizes

Ultrafine aerosol particles with low solubility are generally not present in workplace air as single free particles but as aggregates and agglomerates (U-Prachan). It has been proposed that these aerosols should be temporarily characterised by particle concentration between D-5 and D-200 nanometres, together with an analysis of particle size and mass concentration. The methodology and composition of this U-fraction is analysed for welding fume. Results demonstrate that in this case, ultrafine particles mainly create chain shaped aggregates longer than 1 micrometer (Roedelsperger and Bruekel, 2000). This paper also gives an estimate of the number of ultrafine primary particles in the workplace atmosphere however this paper was not obtained in the time available.

Exposure levels

MMA welding appeared to produce a lower level of aerosol than MIG welding but this was based on one experiment. Measurements made when there was MIG welding activity at the foundry are consistent with the measurements made during the MIG welding operation in the laboratory because similar sized and high levels of ultrafine aerosols were observed. The similarity in the size distribution median diameters of the two aerosols and the number of ultrafine articles they contain is striking. These results indicated that the ultrafine aerosol produced at the steel foundry during the visit was dominated by the MIG welding fume even though this activity was carried out only periodically.

In Sioutas (1999) study aimed at characterizing fine particles (e.g. smaller than about 3μm) in an automotive plant, the average 24-hour mass concentrations of particles smaller than 3.2μm in aerodynamic diameter was 167.8 μg m^{-3} for welding with the mass median diameter being approximately 0.5 μm.

A2.9.6 Soldering

Process

The pyrolysis products of soldering with rosin flux consist of two fractions – particulate (approx. 90% by mass of total fume) and gaseous / vapours (approx. 10% by mass). The actual constituents and quantity of fume depends on the type of rosin in the flux, wire thickness, metal/flux ratio and vary both qualitatively and quantitatively with temperature (HSE, 1997).

The three main techniques for the application of solder are:

- Hand soldering using a soldering iron at 200-450^{0}C when molten solder alloy is applied to the connections of an electric joint.
- Flow (wave solder) soldering when assembled circuit boards which have been pre-treated with a solution of flux are mechanically fed over a ‘standing wave’ of molten solder. This method is used in automated large batch production and is usually enclosed.
- Oven baking when a paste of solder metal and flux is applied to the component connections which are then oven baked to melt the solder.

Fume from hand soldering will rise vertically on thermal currents, entering the breathing zone of the worker as they lean over their work (HSE, 1997). Although rosin is one of the most commonly used fluxes for soldering, other fluxes based on pentaerythritol and water soluble organic acid-glycol bases are available.

Exposure levels

Wake (2001) measured the aerosols produced during hand soldering. This process was undertaken in an area ventilated by a small axial fan. Measurements were carried out with ventilation on because the level of fume was very high without it. On previous occasions when the air extraction was not measured, the maximum particles concentration (10 million particles per cubic centimetre of air) measurable by the SMPS was reached. High levels of ultrafines were observed in the breathing zone for short periods of time. This was thought to be due to the soldering iron being moved momentarily out of the capture zone of the extraction system. With the simple extraction system it was possible to control the levels of ultrafines in the room to levels close to those in the ambient. Without extraction, high levels of ultrafines in the room started to build up. Similarly, as is the case for other processes involving heat, the size distribution median diameter of the fume was slightly higher than that of the ambient aerosol.

A2.9.7 High speed metal grinding

Mechanical processes such as grinding are classically thought to form micrometer scale aerosols through abrasion and attrition. Very little attention has been given to the possibility of mechanical generation leading to substantial aerosol exposure from ultrafine particles. Limited data indicate that it is possible to generate high particle number concentrations from mechanical processes. McCawley *et al (*2001) have shown that the number-weighted aerosol distribution generated while grinding beryllium ceramic was dominated by particles <100nm and Choe *et al* (2000) have shown that dry paint scraping and sanding can lead to substantial particle number concentrations below 1µm. However apart from these studies there is little in the literature to indicate the likely contribution of mechanical processes to ultrafine aerosols in the workplace. Zimmer and Maynard (2002) mechanically ground various substrates including steel, aluminium, hardwood and granite using a hand-held tool in a controlled environment, characterizing the aerosol generated over a particle size range from 4.22nm to 20.5µm. The study found the ultrafine particles were indeed generated for a variety of substrates and there was evidence to suggest that grinding of some substrates produced ultrafine particles through vapourisation or combustion of the substrate material via nucleation. In the absence of a substrate, there was also evidence that the grinding tool itself led to the formation of ultrafine particles, albeit at much lower concentrations. For the steel substrate nanometer sized primary particles within large open agglomerates were observed, whilst for other substrates including aluminium, nanometer size particles could not be discerned.

In Sioutas (1999) study aimed at characterizing fine particles (e.g. smaller than about 3µm) in an automotive plant, the average 24-hour mass concentrations of particles smaller than 3.2µm in aerodynamic diameter was 103.9µg m^{-3} for grinding with the mass median diameter being approximately 0.8µm.

No papers were identified which focussed on operators inhalation exposure during high speed metal grinding or high-energy drilling.

A2.9.8 Depleted uranium

There has also been concern regarding possible occupational exposure to ultrafine depleted uranium (DU) aerosols following the use of DU munitions or where DU has been accidentally or deliberately heated (e.g. during the welding of reclaimed battlefield scrap) due to its pyrotechnic nature.

There is a lack of detailed mineralogical and chemical analysis of material liberated under battlefield conditions (or other conditions in which uranium dust has been liberated following combustion). However, studies which have been undertaken on the use of DU munitions suggest a wide range of particle sizes being formed and these are referenced in WHO (2001). For example, Mishima *et al* (1985) indicated that over 99% of the formed uranium oxide particles were greater than 20µm AMAD and could therefore be considered as being non-respirable, CHPPM (2000) concluded that 60-96% of DU particulate released in and around the vicinity of a target consisting of particle sizes ranging from to 10µm, Bleise *et al* (2003) reports that most of the dust particles produced are smaller than 5μm diameter in size. Aerosols produced during impacts of DU penetrators against the glacis (sloping armour) and the turret of a tank were sampled, with median aerodynamic diameters of 1 and 2 microns being found respectively (Chazel *et al;* 2003). Particles formed inside the vehicle are reported to either adhere to the inside surfaces or be released into the atmosphere through openings. As they accumulate on interior surfaces, the particle size and mass may change due to agglomeration processes (Bleise *et al;* 2003).

No studies were identified where actual occupational exposure to ultrafine aerosols was assessed.

A2.10 References

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APPENDIX 3: ESTIMATING POTENTIAL WORKING POPULATION EXPOSED

A3.1 Introduction

This Appendix provides further information on how estimates of potential working population provided in Section 7. were determined.

A3.2 Estimates of global nanotechnology workers.

It is currently estimated that there are 20,000 individuals working worldwide in nanotechnology today (NNI, 2004). The NanoInvestor News Company Database available at http://www.nanoinvestornews.com/ncd.php, is a database of over 850 nanotechnology companies word-wide. Details of the company's primary location by country were obtained and this is summarized in Table A3.1. Several of these companies may have more than one site, possibly in several countries, however details of these have not been included.

Table A3.1 Number of nanotechnology companies per country (http://www.nanoinvestornews.com/ncd.php)

Country	Number of companies
Australia	11
Austria	1
Belgium	3
Canada	32
China	18
Cyprus	1
Denmark	8
Estonia	1
Finland	5
France	12
Germany	78
Gibraltar	2
Hungary	1
India	3
Ireland	5
Israel	21
Italy	3
Japan	41
Mexico	1
New Zealand	1
Norway	7
Russia	8
Singapore	5
South Africa	1
South Korea	16
Spain	1
Sweden	9
Switzerland	33

Taiwan	13
The Netherlands	9
UK	**40**
USA	473
TOTAL	891

Out of a total of 891 companies, 40 (22%) are based in the UK.

The list was also broken down into industrial sector and this is summarized in Table A3.2. It should be noted that there may be some companies which are involved in more than one aspect of nanotechnology which has not been reported. Details of the names of the companies both by country and industry are available at http://www.nanoinvestornews.com/ncd.php,

Table A3.2 World-wide nanotechnology companies by industrial sector (http://www.nanoinvestornews.com/ncd.php)

Industry	Number of companies
Consulting	14
Consumer Goods	4
Media	3
MEMS	113
MicroSystems	4
NanoBiotechnology	**140**
NanoChemicals	**25**
NanoComposites	2
NanoDevices	134
NanoElectronics	2
NanoEnergy	1
NanoInstruments	141
NanoMachines	3
NanoMaterials	**86**
NanoPowders	**87**
NanoTubes	**45**
Other	5
Photonics	3
Research	**12**
Software	20
TOTAL	891

Of the 891 companies in Table A3.2, 395 (44%) are thought to be involved in some way in the manufacture, development and/or research of nanoparticles (these are highlighted in bold). If nanobiotechnology is excluded this falls to 255 companies (29%). Scott Mize commented at the Foresight Conference, October 2002, that more than 140 companies worldwide were engaged in nanoparticle manufacture at that time and these figures may in fact illustrate the rapid growth within these industrial sectors (ETC group, 2003).

A3.3 UK estimates

As mentioned previously, it is currently estimated that there are 20,000 individuals working worldwide in nanotechnology today (NNI, 2004). If we assume that the UK represents 22% of the market on the basis of Table A1.1, approximately 4,400 individuals are working in nanotechnology within the UK.

A3.3.1 UK nanotechnology companies

The NanoInvestor News Company Database lists 40 nanotechnology companies within the UK. This list only contains details of 6 companies involved in the manufacture of nanoparticles and they have been described previously in Section 5, along with 5 additional nanoparticle companies identified from alternative sources. The ION report 'Nanotechnology in the UK' produced in 2004, covers nanotechnology research activity in the UK, providing profiles of over 100 companies. Unfortunately a copy of this report was only obtained near completion of this review work.

Details of the other companies and their key industrial area out with the general scope of nanoparticles are provided in Table A3.3. Where possible, an estimate of the number of employees within the company is provided (although this may also include sales and office staff). Employee information was only available for two companies involved in the manufacture of nanoparticles. These ranged from 6 to 150. Based on this very limited information we "estimate" that on average there are 78 individuals per company involved in the manufacture of nanoparticles. On this basis it us suggested that 858 individuals are potentially exposed to nanoparticles in the UK.

Table A3.3: List of UK companies and primary industry
(http://www.nanoinvestornews.com/ncd.php)

Company name	Industry	No. employees
Accelrys Inc.	Software	600
Atkina Ltd	NanoDevices / NanoElectronics	
Aquila Instruments Ltd.	Nano instruments	
BTG plc	Nanobiotechnology	
Cientifica Ltd	Consulting	
Exitech Ltd.	Nanoinstruments	
Infinitesima Ltd.	Nanoinstruments	
JR Nanotech PLC	Nanobiotechnology	
Kelvin Nanotechnology Ltd	NanoDevices – NanoElectronics	2
LEO Electron Microscopy	Nanoinstruments	
Malvern Instruments Ltd.	Nanoinstruments	
Mantis Deposition Ltd	Nanoinstruments	
Mesophotonics Ltd	Photonics	
Micro Chemical Systems Ltd	Research	14
Microsaic	MEMS	
Nanograph Systems Limited	Nanoinstruments	
NanoMagnetics Instruments Ltd.	Nanoinstruments	
Nanomagnetics Ltd	Nanodevices	15
NanoSight	Nanoinstruments	
Nanotecture Ltd	Nanodevices	
Obducat CamScan Ltd.	Nanoinstruments	
Orla Protein Technologies Ltd.	Nanobiotechnology	
Oxford Applied Research	Nanoinstruments	
Oxford Biosensors Ltd	Nanobiotechnology	
Oxford Instruments plc	Nanoinstruments	1500

Plastic Logic Lit	Nanodevices	
Polaron CVT & Oxford NanoScience	Nanoinstruments	
QinetiQ Group PLC	MEMS	
Radar World Ltd	Nanoinstruments	
Semefab Ltd.	MEMS	
Sense Proteomic Ltd	Nanobiotechnology	20
Sifam Instruments Ltd	Nanoinstruments	
Olexa Ltd	Nanobiotechnology	
Surface Technology Systems plc	MEMS	195

A3.3.2 UK Research and University Institutions

The main research and university centres of nanotechnology expertise in the UK were identified through web searches. We identified a total of 37 centres. These are listed in Table A3.4 along with details of their research interests. Information on personnel involved was also obtained from the web searches and this is also summarised.

Table A3.4: Main research and University centres of nanotechnology expertise in the UK

Name	Interests	No. of personnel
Daresbury Laboratory and Rutherford Appleton Laboratory	Includes research into new materials and structures	550 and 1200 respectively
Heriot Watt University	Information not immediately identifiable	
Imperial college of science, technology and medicine	Projects include: Electrically addressable nano-structured cells; Microstructures for nanoscale measurement; Advanced MEMS for MM wave communications.	27
Queens University, Belfast and University of Ulster and various industries *Nanotec NI - Northern Ireland's Nanotechnology research, development and exploitation centre.*	Design, fabrication, characterisation and commercial exploitation of nanotechnology processes, devices and systems.	150 (represents significant block of research capability across the UK)
University College London *The London Centre for Nanotechnology (LCN) – spring 2004*	Fabrication research, theory and modelling, experiments on chips and tips, novel electronics, nanobiology, studies of nanofluids and nanomagnetism.	52
University of Cambridge	Research varied:design and engineering of proteins for use in functional nanostructure, applications of fullerene-based materials to nanoelectronics and quantum computation; local properties of filled carbon nanotubes and other.	23 senior research staff

	nanostructures, nanofabrication using electron beam nanolithography, fabrication and characterisation of nanometre scale structures and devices etc.	
University of Liverpool The Centre for Nanoscale Science	Nanoscale materials and devices (optical, magnetic, electronic and sensors) and bioanalytical applications of nanotechnology.	18
University of Manchester	The goal of the centre is to create an easy-to-access-and-use, multidisciplinary workshop that allows researchers to fabricate, visualise and characterise nanostructures and devices	9
University of Newcastle Upon Tyne The Institute for Nanoscale Science and Technology and commercial arm - 'INEX: Nanotechnology Exploitation'	Continuous link from generic research through to materials, engineering and device fabrications support and clinical testing of prototype systems and devices.	100 in total
University of Paisley Scottish Centre for Nanotechnology in Construction Materials	Enhancement of fundamental knowledge and practical performance of basic and new construction materials.	6
The University of Glasgow	Nanoelectronics and Nanofabrication	
University of Cranfield	Fusing microengineering and nanotechnology with the industrial application and development of ferroelectric materials and devices.	33
University of Durham	Conductive Polymers and Charge-Transfer Compounds, Nanoparticles, Molecular Recognition, Nanoelectronics etc.	15
Royal Holloway University of London	Development of techniques to fabricate small feature sizes in increasingly complex materials (principally metals, but also semiconductors) in order to explore quantum effects at submicron length scales.	15
University of Sussex	Work covers several different fields including nanotube production & modification, development of new ways of coating nanotubes with ceramics, polymers and fullerene chemistry manipulation.	25

IRC in Nanotechnology collaboration between the University of Cambridge, University College London and the University of Bristol	Objectives include growth of soft layers by directed self-assembly on patterned substrates, determining mechanical and electronic properties of nanoscale interfaces, spinning out several projects into the commercial sector.	
Lancaster University	Nanocharacterisation of the basal lamina for tissue engineering, specific applications of nanotechnology and their ethical and socio-political issues.	
University of Bath	Includes development of special carbon structures and porous oxides and structured adsorbents, novel materials for reactive separations and catalysis, nanomaterials.	24
University of Birmingham	Investigation into the role of Focused Ion Beam (FIB) Technology in the Fabrication of MEMS devices, Micro Wankel Engine, Rapid Mixing Micromixer for Drug Discovery Purpose.	13
University of Bristol	Research includes: Photoelectrochemistry of Quantum Dots, Templated Synthesis of Nanoparticle, Quantum Dot Sensitised Solar Cells and Deposition of Nanoparticles at Surfaces.	13
University of Dundee	Information not immediately identifiable	
DeMontfort University	Information not immediately identifiable	
University of Edinburgh	Research includes: Directed growth of carob nanotubes, nanocluster science, smart biomolecular machines, nanoporous fluids and behaviour within them, MEMS etc.	
University of Glasgow An interdisciplinary research centre (IRC) in Bionanotechnology is currently being established between the universities of Oxford, Glasgow, and York.	Aim to combine expertise to develop new technology that will enable the manipulation and characterisation of single biological molecules. In particular, we are developing single molecule imaging and manipulation techniques for the purpose of exploring the structure and function of molecules supported artificial bilayer membranes.	14
University of Leeds	Information not immediately identifiable	
University of Leicester	Information not immediately identifiable	

University of Nottingham	Nano-scale analysis, Fullerenes, Nanoelectronics and optoelectronics, Nanoparticles , Nano-structured thin films, Nanoporous materials, Nano-manipulation and patterning, Bio-nanotechnology.	
University of Portsmouth	Information not immediately identifiable	
University of Reading	Fostering research programmes in the areas of nanostructure research, experimental and theoretical surface science and cluster and particulate research.	12
University of Southampton	Information not immediately identifiable	
University of Sheffield *working in partnership with Leeds and York University*	Semiconductor nanotechnology, nanosizing chemistry, soft nanotechnology, nanomagnetism and nanostructured materials, nanocharacterisation and tissue engineering.	
University of Strathclyde	Information not immediately identifiable	
University of Wales, Aberystwyth	Information not immediately identifiable	
University of Warwick	Information not immediately identifiable	
University of York	Information not immediately identifiable	

On the basis of the information available from the University and research centre web sites, we identified approximately 2300 workers involved in some way with nanotechnology. If it is assumed that 5 individuals work in nanotechnology for each of those centres where no personnel figures were provided, the total estimated figure is approximately 2400.

The ION (2004) review estimates that approximately 1500 researchers are currently employed in UK University and Research centres involved in nanotechnology. In a survey of 12 research institutions, employing 1200 researchers; 440 were found to be PhD students, 350 post doctorates and 330 tenured staff. Of the 14 surveyed only 3 had more than 100 staff employed in nanotechnology research, 6 had 50 to 100 employees with the remaining claiming to have 29 to 50 employees.

A3.3.3 Existing ultrafine processes

There are relatively few existing manufacturing processes in the UK which produce ultrafine products. For commercial products such as ultrafine TiO_2 and zinc oxide used in this country by the cosmetics industry, production is confined to Europe, USA and Canada (Wake, 2001). ONS (2003) reports that 255,000 individuals are employed in the sector ‘manufacture of chemicals, chemical products ands man-made fibres’, which includes a multitude of different chemicals and processes and it is difficult to estimate what proportion of these individuals would actually be exposed to ultrafine aerosols. However, where possible estimates of the number of companies and / or potential numbers of employees involved in processes where ultrafine aerosols may be present are provided in the following sections. However, given that it is not always possible to establish what proportion of these individuals are process operatives, sales or office staff, these figures should be viewed as being worst case figures unless otherwise stated.

Carbon Black manufacturing

In the United Kingdom, only two factories manufacture carbon black, one of which uses the furnace black process alone, whilst the other uses both the furnace and thermal black processes. Approximately 300 people are employed in the production of carbon black in the United Kingdom (IARC, 1996) though it is unknown whether all of these would potentially be exposed to ultrafine aerosols.

Production of high surface precious black metals

The production of high surface area precious black metals was found in one company to only involve 1 to 2 people (Wake, 2001). ONS (2003) reported that 2,000 individuals were involved in precious metal production in 2001. This includes the production and refining of gold, silver, platinum metals, alloys and semi-products. On this basis it is suggested that no more than 50 will be exposed to ultrafine aerosols during production.

Ultrafine Titanium Dioxide manufacturing

The limited search revealed that there are no ultrafine titanium dioxide manufacturing sites within the UK.

Fumed Silica manufacturing

No UK manufacturing sites for fumed silica were identified.

Fumed alumina manufacturing

ONS (2003) reports that in 2001, 12,000 individuals were employed in the sector ‘aluminium production’ which includes the production of aluminium oxide (alumunia), production of aluminium from alumina, production of aluminium from refining of waste and scrap, production of alloys and semi-manufacturing of aluminium. Only a small proportion of this concerns the manufacturing of aluminium powders and only a proportion of that will be fumed alumina. ONS (2001) reports that in the UK, in 1999, manufacturer sales of aluminium were £1,800M and the sales of powders and flakes were £16M, less than 1%. On this basis it is reasonable to suggest that not more than 1% of the workforce is involved in the manufacture of these products. This would indicate a maximum of 120 workers potentially exposed during production of these materials.

Pharmaceutical industry

It is estimated that there are 65,000 people directly employed in the pharmaceutical industry in the UK (Scott, 2003). ONS (2003) estimated that on average, 71,000 individuals were employed in the sector the ‘manufacture of pharmaceuticals, medicinal chemicals and botanical products’ throughout the year 2001. It can be assumed that the sales forces accounts for 20% of the workforce (Scott, 2003).

Various powder handling processes

Carbon black

In a postal survey carried out by the Institute of Occupational Health (IOH), of the 1549 companies who received the questionnaire, 524 responded and 139 of these reported using carbon black. Completed questionnaires were received from 64 companies. Table A3.5 gives information collected, via the questionnaire, on the number of companies and the number of workers involved in the use of carbon black (IARC, 1996).

Table A3.5: Number of companies and workers involved with use of carbon black and use of carbon black per year by industrial sector from IOH questionnaire.

Industry	No. of companies	No. of workers
Chemicals	4	187
Distributors	1	6
Pigments	13	128
Plastics	8	185
Printing inks	11	114
Rubber	23	409
Miscellaneous	4	20
Total	62	1049

However, information provided by the British Rubber Manufacturers Association (BRMA) indicates that there are 7 companies manufacturing tyres, with approximately 250 people potentially exposed to carbon black, and 30 companies (generally SMEs) manufacturing general rubber goods in Great Britain (personal communication). Other uses of carbon black include pigments in printing inks, photocopier toners, coatings, plastics, fibres, paper and in batteries. There are still at least two manufacturers in Great Britain that use carbon black in the production of the batteries (IARC, 1996).

It is estimated that the total numbers potentially employed in the use of carbon black is likely to be upwards of 2,000 people.

Ultrafine Titanium Dioxide

Wake (2001) noted that there is only one UK company, that buys and handles ultrafine TiO_2 for direct formulation into cosmetics and lotions such as sun block. No details on company size or numbers of individuals exposed were provided therefore it is assumed that 50 individuals in total are exposed.

Cement

ONS (2003) estimated that 4,000 individuals were involved in the manufacture of cement during 2001. This includes the manufacture of Portland, aluminous slag and superphosphate cements and excludes the manufacture of cements used in dentistry, manufacture of refactory mortars and cements and ready-mixed.

Paint

ONS (2003) estimates that 28,000 individuals were involved in the manufacture of paints, varnishes and similar coatings, printing inks and mastics in 2001.

Pigments and dyes

ONS (2003) estimates that 11,000 people were involved in the manufacture of dyes and pigments from any source in a basic form or concentrate in 2001.

A3.3.4 Ultrafine by-products

Thermal spraying and coating

It has been reported by ONS (2003) that 25,000 individuals were employed in the treatment and coating of metals which includes the plating, anodizing of metals, heat treatment, sand blasting, colouring, engraving, non metallic coating and buffing in 2001. However it is not known how many of these would only be involved in thermal spraying and coating.

For thermal spraying and coating, Wake (2001) noted that although the factory surveyed employed 20 people, most employees worked in the office on the packaging lines, with only five people being directly involved with the spraying operations.

Zinc refinery

ONS (2003) reports that 2,000 people were employed in the lead, zinc and tin production sector in 2001. This includes those involved in the production of these metals from ores, from waste and scrap, the production of alloys and semi-manufacturing of the three metals. If we assume that only a third of these individuals were involved in the production of zinc and of these, only a seventh actually worked within the plant (350/50 from numbers reported by Wade, 2001), the number of people potentially exposed is estimated to be just under 100.

In a zinc refinery visited, about 350 people were employed however only approximately 50 people actually worked in the plant and these were mostly in the refinery and metal stores (approximately 20 employed in the latter area) (Wake, 2001).

Steel refinery

ONS (2003) reported that 30,000 individuals were involved in the manufacture of basic iron and steel and of ferro-alloys in 2001. This includes the production of pig iron and steel from ore or scrap reduction, production of steel from a furnace, ferrous items from iron ore and so forth. ONS (2003) also reports that 5,000 people were employed in the casting of steel castings, finished or semi-finished products in 2001. Smillie *et al* (1994) noted that 20% of the workforce within this industry includes job categories such as sales, clerical and office staff who would probably not work in areas where ultrafine aerosols may be present. Therefore it is estimated that 28,000 may be exposed (35,000 - 20% = 28,000).

In a steel foundry visited, approximately 40-50 people were employed, with approximately 10 people working in the foundry at any one time (Wake, 2001).

Aluminium refinery

As mentioned earlier, ONS (2003) reports that in 2001, 12,000 individuals were involved in aluminium production which includes the production of aluminium oxide (alumunia), production of aluminium from alumina, production of aluminium from refining of waste and scrap, production of alloys and semi-manufacturing of aluminium.

Wake (2001) noted that there is at least one primary aluminium smelter in the UK. Seven secondary aluminium smelters were visited in the survey and approximately 3-5 people were exposed in each of these with 10 being exposed in one factory.

Nickel refinery

ONS (2003) reports that 4,000 people were employed in the production of other non-ferrous metals including chrome, manganese as well as nickel from ores / oxides, wastes and scraps. It also includes the manufacturing of alloys, mattes of nickel and semi-manufacturing of these metals.

Metals casting

ONS (2003) reports that 30,000 people were employed in 2001 in the casting of metals such as iron, steel, light metals and other non-ferrous metals which were not undertaken during the direct manufacture of the metals as previously mentioned.

Metal grinding and welding

It has been reported by ONS (2003) that 391,000 individuals were involved in the manufacture of fabricated metal products, except machinery and equipment in 2001. Of these, 35,000 were employed in forging, pressing, stamping and roll forming: powder metallurgy which includes forging, pressing, powder metallurgy, production of metal objects directly from metal powders by heat treatment or under pressure. 25,000 were employed in the treatment and coating of metals which includes the plating, anodizing of metals, heat treatment, sand blasting, colouring, engraving, non metallic coating and buffing. 108,000 were employed in 2001 in general mechanical engineering which includes boring, milling, eroding, sawing, grinding, welding, splicing of metal work pieces. It is estimated that there are approximately 40,000 individuals involved in welding in the UK, (Northage personal communication) and ONS (2003) estimates that 1,000 individuals in 2001 were involved in the manufacture of steel tubes by various hot and cold processes and welding.

Another 39,000 individuals were involved in the manufacture of cutlery, tools and general hardware, 82,000 other fabricated metal products and 366,000 in the sector ‘manufacture of machinery and equipment not elsewhere classified’.

Soldering operations

Soldering is carried out in a large number of firms, ranging from companies with many people soldering to small companies who only employ 1 or 2 solderers. For this reason it is difficult to estimate how many people are occupational exposed to solder fume but it may be upwards of 50,000. A large number of people, including plumbers and telephone engineers, may also do some soldering as part of their job. This intermittent type of work may lead to short-term high exposures.

Other sources of ultrafine particles

Attempts to suggest numbers of individuals potentially occupationally exposed to ultrafine aerosols from sources such as vehicle exhausts, combustion processes have not been made.

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