Health & Safety Executive NanoAlert Service

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Bulletin Contents:

1. MEASUREMENT, EXPOSURE AND CONTROL

In this bulletin, the search included a comprehensive search of the literature as described in Issue 1 and an additional search from specific relevant journals. Those articles considering engineered nanoparticles were assigned a higher priority than those related to ambient ultrafine particles. A breakdown of the number of papers per topic is shown in Figure 1. As observed in previous bulletins, a significant number of papers and abstracts are being published on the development, improvement and assessment of instruments for the measurement of airborne nanoparticles. One can also start to observe the emergence of papers reporting on the design and development of compact monitors, which are much sought after by occupational hygienists. As observed in previous bulletins, very few studies on the assessment of exposure levels to engineered nanoparticles in the workplace have been published in peer-reviewed journals. However a number of studies are currently being undertaken and early data may be obtained from conference proceedings. The same observation can be drawn on engineering control measures. A number of papers have been published reporting on the efficiency of filters but no studies on face-fit testing of respirators.

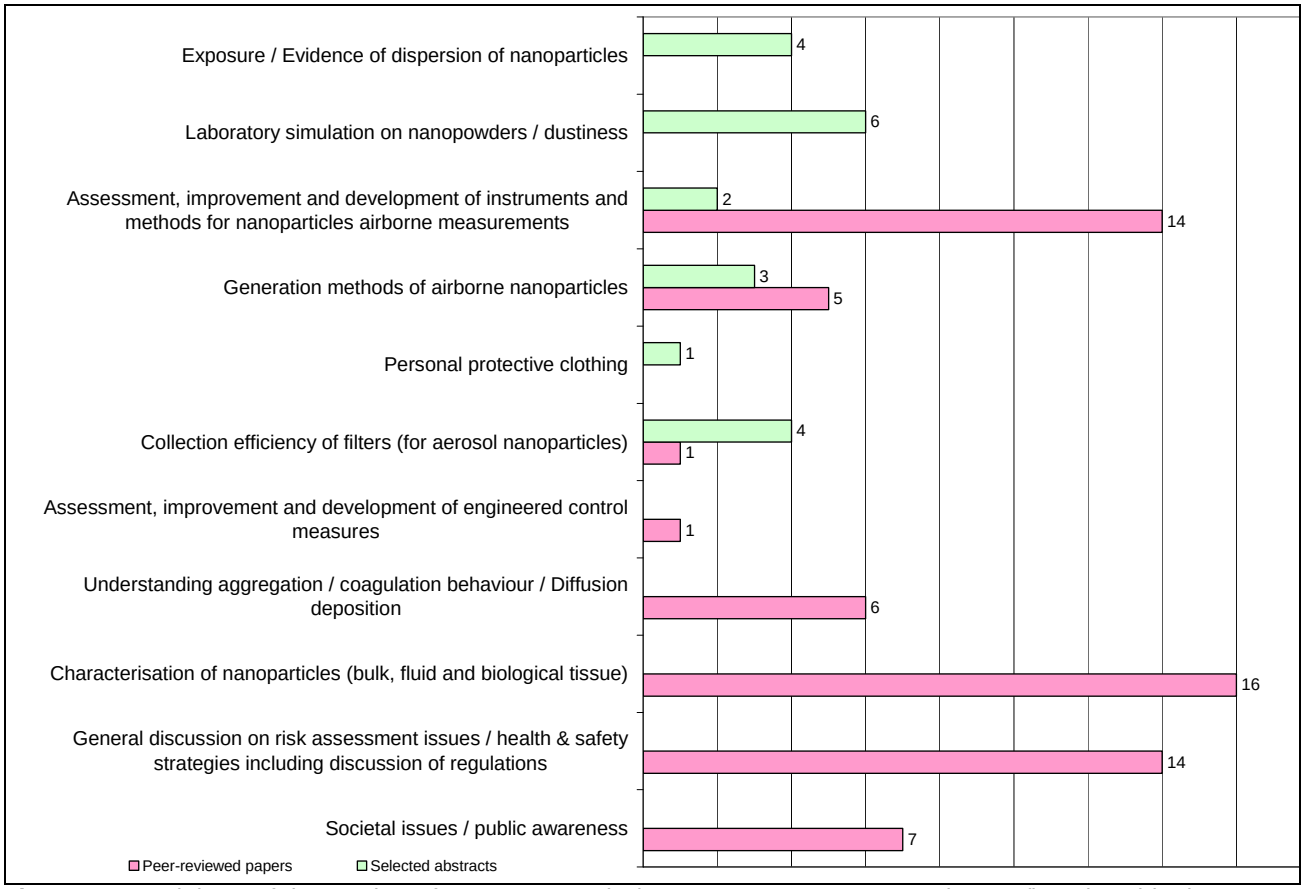

Figure 1: Breakdown of the number of papers per topic (measurement, exposure and control) retrieved in the four months from July to October 2007.

1.1 Exposure data

Workplace exposure

Toxicology studies have suggested that the monitoring of nanoparticles exposure against mass concentration alone is not sufficient and it is necessary to measure the level of particles in terms of surface area and number concentrations. Recent studies have usually included measurement of all three metrics.

As observed in the previous bulletins, very few studies on the assessment of exposure level to engineered nanoparticles in the workplace have been published in peer-reviewed journals. However a number of studies are currently being undertaken and have been presented at the third International Symposium on Nanotechnology, Occupational and Environmental Health in Taipei (Taiwan, 2007). The abstracts reported **measurements at production plants and at universities or research laboratories:**

Workplace exposure characterisation at TiO_2 nanoparticle production. Berges M et al (**Conference abstract**, 2007) [1]

The authors carried out workplace exposure measurements at different TiO_2 nanoparticle processes. The number concentrations were monitored using a Scanning Mobility Particle Sizer and the Aerodynamic Particle Sizer, the surface area concentrations using the Nanoparticle Surface Area Monitor and the mass concentrations using a low-pressure impactor. The abstract reported measurements at the bag filling station. The authors found that:

- The total number concentrations was between 15,000 and up to 156,000 particles/cm^3 (size range of 14 to 673 nm) with the maxima at 20 – 30 nm. The higher concentrations were due to a leak. After the leak was closed, the concentration decreased to less than 29,000 particles/cm^3 with the maxima at 20nm.
- The inhalable and respirable mass concentrations were 0.232 mg/m^3 and 0.1 mg/m^3 respectively.
- A personal sampler on an employee working in this area showed a respirable dust concentration of 0.141 mg/m^3.
- The surface area concentrations showed values up to 200 $\mu m^2/cm^3$ for the alveolar deposit and 50 $\mu m^2/cm^3$ for the tracheo-bronchial deposit near the leakage and 50 $\mu m/cm^3$ and 13 $\mu m^2/cm^3$ at normal operation.
- The total number concentration of environmental ultrafine particles outside the plant was approximately 13,000 particles/cm^3.

Airborne nanoparticle concentrations in a nanotechnology workplace. Singh M et al (**Conference abstract**, 2007) [2]

The authors carried out measurements at a commercial nanomaterial manufacturing facility. The number concentrations were monitored using a Scanning Mobility Particle Sizer and a Condensation Particle Counter, the surface area concentrations using the AeroTrack nanoparticle aerosol monitor and the mass concentrations using the DustTrack aerosol monitor. The abstract reported measurements of the concentrations of nanoparticles near the vicinity of a large furnace used for the calcination of an intermediate material. The authors found that:

- A gap in the exhaust system led to the leaking of a large number of nanoparticles. The concentrations ranged between 105,970 to 135,700 particles/cm^3 with the majority of particles having a diameter less than 30nm.

- The lung deposited surface area concentrations ranged between 16.7 $\mu m^2/cm^3$ and 25.5 $\mu m^2/cm^3$.
- The mass concentrations were less than 20 $\mu g/m^3$.
- Two other work areas close to material handling operations were monitored but the results were not reported in this abstract.

Occupational health and safety field study of quantum dot nanomaterials. Methner M et al (**Conference abstract**, 2007) [3]

The National Institute for Occupational Safety and Health (NIOSH) has carried out measurements at a small quantum dot research and development facility during creation and manipulation of cadmium quantum dots. "Engineered and personal control used included: single-pass laboratory hoods; positive pressure glove box; class 10,000 clean room; nitrile gloves; safety glasses; disposable cotton laboratory coats; disposable Tyvek™ laboratory coats (for clean room); a partially enclosed weighing station connected to a high efficiency particle air (HEPA) filtered exhaust system; "sticky mats" at all doors leading to from the laboratory area".
Surface and filter samples were collected using:

- For surface samples: Surface wipe samples (Ghost wipe™ pre-moistened towels – NMAM method 9102) and surface sample swabs from CadmiumCheck™ surface sampling kits.
- For air samples: high flow pumps at a sample rate of 7 l/min and 37 mm 0.8 µm pore size mixed cellulose ester membrane filters (for Transmission Electron Microscopy (TEM) analysis).

Real time concentration measurements were carried out using a condensation particle counter (CPC) and a laser light scattering instrument.

The abstract reported that:

- None of the eight air filter samples collected at four different locations within the laboratory (fume hood; glove-box; microscopy laboratory; clean-room) was positive for cadmium or showed microscopy evidence of quantum dots.
- No substantial increase in particle concentration was measured using real-time instruments.
- No evidence of gross contamination in air or surface samples was detected.
- Very low (<1µg) amounts of cadmium were detected on a few surfaces.

Workplace airborne nanoparticle exposure measurement at university research centers. Tsai S-J (C) et al (**Conference abstract,** 2007) [4]

The authors carried out measurements using a Fast Mobility Particle Spectrometer (FMPS) at various research laboratories in the USA, for seven process types (e.g. electro-spinning, compounding, carbon nanotube furnace, fullerene reaction, twin screw extruding, silica handling and carbon black handling) and 20 operations. Measurement at background locations, source locations and operator breathing zone were obtained and some airborne samples were collected for electron microscopy analysis. The abstract reported that:

- During a compounding process of polymer beads and nanoalumina particles, the breathing zone concentration and size distributions were significantly different from the background due to the absence of proper local exhaust ventilation. Particles number

concentrations (up to 150,000 particles/cm^3 at a particle size of 200 nm and up to 20,000 particles/cm^3 for particles less than 50nm) were measured at source locations.

- During the synthesis of single wall carbon nanotubes (SWCNTs) by chemical vapour deposition, high particle concentration on the exhaust air (up to ~ 11,000,000 particles/cm^3 at a particle size of ~ 50nm) was measured. There was no indication in this abstract whether some characterisation had been carried out to determine if this concentration was associated with SWCNTs or by-products or both. Nevertheless, very low concentration at the operator breathing zone (not estimable on the graph) was measured. The device had been placed in a fume-hood.

In these four abstracts, there is no indication whether background ultrafines have been subtracted from workplace exposure concentrations and therefore it is doubtful that these measurements represent personal exposure to nanoparticles alone.

Laboratory simulation

An abstract on the investigation of potential exposure to nanoparticles from simulated tasks under laboratory conditions has been published:

Evaluation of aerosol release during high-energy ball milling of metallic oxide powders. Witschger O et al (**Conference abstract,** 2007) [5]

The authors have assessed under laboratory conditions the potential exposure to nanoparticles during the high energy milling of metallic oxide powders. Several scenarios were investigated:

- handling of powders prior to and after milling (in a laboratory)
- leaks during milling (in a laboratory)
- unintentional spills of nanopowders (in a glovebox without air circulation)

The abstract reported some of the results:
The authors found respirable mass concentrations of 37.0 $\pm$ 0.5 µg/m^3 using sampling on filters with a size selective sampler CATHIA. Particle number, tracheobronchial active surface area and mass concentration were also measured.

Agglomeration / nanopowder behaviour

The dustiness behaviour of nanoparticles is an important property. For materials, where nanoparticles do not become readily airborne under normal handling procedures, the associated risk from inhalation will be considerably reduced. Dustiness testing enables the investigation and quantification of the propensity of a powder to become airborne when handled. In 2006, the European Committee for Standardization (CEN/TC137/WG3) produced a document providing standardisation in measurement of dustiness of bulk powders (EN15051) [6]. This standard establishes two reference test methods (single drop or rotating drum method) that classify dustiness in terms of health-related fractions of bulk solid materials. A number of questions arise when testing nanopowders compared to micron powders. **Is mass the most appropriate metric for nanoparticles or should particle number or surface area be measured? Should dustiness still be assessed in terms of health related fractions especially for agglomerated nanoparticles?**

A number of modified approaches from the testing of micron powders have been presented at the third International Symposium on Nanotechnology, Occupational and Environmental Health in Taipei (Taiwan, 2007):

Dustiness tests of fine - and nanosize powders using a small 5.9 litre rotating drum. Schneider T and Jensen KA (**Conference abstract**, 2007) [7]

The authors have developed **a bench-top experimental set-up in which both single drop test and rotating drum test** (cylinder length: 23 cm; internal diameter: 16.3 cm; volume flow of 11 l/min) can be performed using small amounts of samples. The rotation tests were carried out at a rotation speed of 11 revolutions per minute for 1 minute. The authors tested six nano and fine particle powers. Particle number distribution and mass concentration were measured. The authors found that:

- The powders ranked similarly using both tests (rotating drum and single drop method)
- Most of the samples produced a bimodal or multimodal size distribution with the finest mode showing a peak at 100 and 200 nm, except for TiO_2 pigment where no particles were detected below 500 nm.
- Ultrafine TiO_2 has much higher level of dustiness compared to pigment grade TiO_2, releasing 8333 ± 233 mg/kg and 31 ± 21 mg/kg respectively. The dustiness of other powders varied between 283 ± 43 mg/kg (YZR zirconia) and 1710 ± 206 mg/kg (bentonite). These values are related to filter measurements.

Study of nanoparticle emission from nanopowders using a rotating drum dustiness tester. Tsai C-J et al (**Conference abstract**, 2007) [8]

The authors **modified the standard rotating drum method described in EN 15051 (2006)**. A scanning mobility particle sizer (SMPS) and a MSP MOUDI (micro-orifice uniform deposit impactor) was connected to the drum after the second size selective metal foam to measure the number and mass distribution of the respirable fraction. TiO_2 nanopowder (P25 Degussa) was tested in the 300 mm diameter drum, at a rotation speed of 38 revolutions. The authors found that:

- The average inhalable, thoracic and respirable fraction for TiO_2 was 6713, 722 and 15 mg/kg respectively.
- The MOUDI data showed a bimodal mass distribution at 3.2 – 5.6 μm and 0.32 – 0.56 μm in aerodynamic diameter.
- The SMPS showed low total number concentration in respirable dust fraction for particles less than 100nm.

Some considerations for the measurement of the dustiness of nanopowders. Mark D et al (**Conference abstract**, 2007) [9]

- The authors **modified the standard rotating drum method described in EN 15051 (2006)** by inserting a stainless steel sampling tube through the entry filter on the axis of the drum. The tube was connected to either a condensation particle counter (CPC) or a scanning mobility particle sizer (SMPS) for the measurement of particle number concentration and size distribution. Four nanopowders have been tested and the authors found that:
- The respirable dustiness fraction varied from 20 (for anatase TiO_2) to 240 (for CeO_2) mg/kg. The thoracic fraction varied from 60 (for anatase TiO_2) to 4940 (for aluminium oxide) mg/kg. The inhalable fraction was between 610 (for anatase TiO_2) and 11230 (for aluminium oxide) mg/kg.

- The powder substantially agglomerated.

Two other abstracts have been published in the proceeding abstract of the third International Symposium on Nanotechnology, Occupational and Environmental Health (2007).

- Ibaseta N et al (Conference abstract, 2007) reported on an experimental **set-up based on free falling** [10]**.** The test consisted of a chamber (200 x 50 x 80 cm^3), a storage box and a vessel below the storage box, which rotates and vibrates. The size number distribution and calculated mass concentration of the aerosol generated in the chamber was measured using an Electrical Low Pressure Impactor (ELPI). The authors investigated the influence of the variation in the falling height for two nanopowders. They concluded that the aerosol size distribution was independent of the height but the mass concentration depended on the falling height.

- Isamu O et al (Conference abstract, 2007) have used a **set-up made of a vortex shaker fluidized bed and two cyclones** (10μm and 2.5 μm cut size) [11]. The aerosol generated in the glass tube was characterised in term of number concentration and size distribution using a range of real-time instruments (aerodynamic particle sizer, optical particle counter, scanning mobility particle sizer condensation and condensation particle counter). The authors found that for most nanomaterials, the modal diameter was greater than 100nm but a certain number of particles less than 100nm were measured. In general, the number concentrations increased with the level of agitation.

There is a strong need for international collaboration and standardisation of dustiness testing of nanoparticles.

1.2 Measuring and monitoring of airborne nanoparticles

Until it has been agreed which are the most appropriate metrics (such as mass, number, surface area) for assessing exposure to nanoparticles in relation to potential adverse effects, a range of instruments may be required to fully characterise and monitor release of nanoparticles in the workplace. A number of papers have been published on the evaluation and development of such instruments. One can also start to observe the emergence of papers reporting on the design and development of compact monitors, which are much sought after by occupational hygienists.

Evaluation of instruments or methodologies

It is important that the performance and detection limit of instruments used in workplaces for assessing exposure to airborne engineered nanoparticles are investigated.

Particle counting efficiencies of new TSI condensation particle counters. Hermann M et al (2007) [12]

The authors reported on the counting efficiencies of several particle condensation counters (CPC) in the size range from 3 to 40nm for silver and sodium chloride nanoparticles. Water-based CPCs ((WCPC3785; WCPC3786) and butanol-based CPCs (CPC3772; CPC3775: CPC3776) were evaluated. They found that for a given CPC model, the counting efficiencies measured using two different data acquisition systems (pulse output and serial output) can sometimes differ.

The differential mobility analyser (DMA), which separates particles according to their electrical mobility, is widely employed for the sizing and classification of airborne nanoparticles. Theoretical or numerical models are being developed to investigate the performance and response of the DMA. Two papers related to the development of such models have been identified:

Understanding ion-mobility and transport properties of aerosol nonowires. Kim SH et al (2007) [13]

The authors have developed a theoretical model to describe the behaviour of nanotubes or nanowires undergoing Brownian rotation in an electric filed in order to predict their behaviour when travelling through a DMA. Fibrous aerosol particles can be described by a diameter and a length and are difficult to characterise using a DMA. Based on the theoretical model and its comparison with experimental results, the authors found that:

- The orientation of nanowires is strongly dependent on the applied electric field strength and the nanowires aspect ratio.
- Shorter nanowires (aspect ratio less than approximately 30) for a 15 nm diameter tend to rotate freely for applied electric field up to about 1 kV/cm.
- The degree of alignment by the electric field of longer nanowires (aspect ratio greater than approximately 30) increased with increasing the electric field strength.
- Due to the bent structure of the nanowires, the theoretical model over estimated the length for nanowires by 40 – 50% for 600 to 1000 nm nanowires and by 15 – 30% for longer nanowires.

The authors claim that this model can be used "to convert a mobility size distribution into a length distribution of aerosol nanowires with uniform diameter in the free molecular regime".

Mamakos A et al (2007) have investigated the validity of Stolzenburg's transfer function model [14]. The transfer function of a DMA (transmission efficiency of particles as a function of their mobility) is useful to interpret its performance. In general, the transfer function cannot be determined experimentally and an analytical or numerical model is required. The authors have reported that:

- this model is "reasonably accurate over the entire size range of TSI 3081 and TSI 3085 DMA models at a sheath/sample ratio of 10/1" and particle losses in the classification region were also minimal especially under a fully developed laminar flow.

Development of instruments and methodologies

A number of papers on the development or improvement of instruments (more compact, better resolution, multifunctional, faster response, improved charging performance) for exposure measurements of nanoparticles have been published.

Development of compact instruments

There is inadequate portable instrumentation for the measurement of nanoparticles exposure. New sampling techniques and strategies for exposure assessment in the workplace are desperately needed.

Theory and design of a new miniature electrical-mobility aerosol spectrometer. Ranjan M and Dhaniyala S (2007). [15]

The authors present the design of a new miniature electrical mobility aerosol spectrometer (MEAS) of compact size for real-time particle size distribution measurement. The new instrument has a rectangular cross-section with two main regions:

- An electrostatic precipitator section (ESP) from where charged particles are injected into the classifier section.
- A classifier section where particles are separated based on their electrical mobility and collected onto plates connected to electrometers.

The authors reported the theoretical and numerical analysis of MEAS and concluded that "an optimal domain exists for MEAS".

Electrical nanoparticle monitor based on escaping - current technology (ECT). Janka K et al (**Conference abstract,** 2007) [16]

In this abstract, the authors reported an alternative solution of electrical nanoparticles monitor based on escaping current technology (ECT). In this design, the current escaping the charger with the particles is measured and the charged particles are not collected onto a filter, which enable high flow rate through the sensor and high sensitivity. Furthermore, the initial charging state of the particles to be measured does not affect the measurement results. According to the authors, the property measured by the instrument is closely related to the active surface area of the particles. This new design could enable the development of low cost or small and sensitive monitor.

Development of instruments with improved resolution

Nanoparticle cross-flow differential mobility analyzer (NCDMA): Theory and design. Song DK and Dhaniyala S (2007). [17]

The authors present a new differential mobility analyser (DMA) design (Nanoparticle cross-flow differential mobility analyzer: NCDMA) for high resolution classifying of charged nanoparticles. In the conventional DMA, the diffusional effect on small particles reduces the performance of the classifiers. This new NCDMA uses a non-uniform flow field to minimise particle spatial spreading (due to Brownian diffusion) in the DMA. The NCDMA performance was theoretically and numerically studied. The authors suggested that the NCDMA design could provide a higher resolution than a Nano-DMA.

Development of fast response instruments to size particles by their electrical mobility equivalent diameters.

Fast response instruments could be very valuable when measuring exposure to engineered nanoparticles in workplaces from processes likely to generate random and short time scale high concentrations.

A multi-channel electrical mobility spectrometer with wedge geometry-design and first evaluation. Box S and Collings N (2007). [18]

The authors report on the development of a multi-channel electrical mobility spectrometer with wedge-shaped classifier geometry. It is designed to make fast on-line measurement of

lognormal size distribution and number concentration of airborne particle in the size range from 5 to 300nm. The classifier was simulated numerically and the model was used to predict the classifier transfer function. Test aerosol of sodium chloride nanoparticles was generated to experimentally evaluate the charger and the performance of the spectrometer. The authors concluded that the concept of the wedge-shaped spectrometer is viable however improvements have to be made and problems (including high particle losses) to be solved.

Development of multifunctional instruments

As shown by Wake D (2006), the relationships between the mass, number and active surface area concentrations of particles of different morphology may not be a simple relationship [19]. Therefore, a range of instruments has to be deployed at workplaces to assess exposure levels of all three metrics and in an ideal world a single instrument measuring all three metrics at once would be very usefulness.

The differential mobility analyser (DMA) measures the electrical mobility diameter of airborne particles. For spherical particles, the electrical mobility diameter is equal to the particle volume equivalent diameter. For non-spherical particles, the electrical mobility diameter cannot be directly used to measure the equivalent surface area and volume. Wang C-S and Friedlander SK (2007) present a method for the calculation of the total surface area and volume of nanoparticle aggregates deposited in the human respiratory using size distribution data measured with a DMA [20].

Improvement of charging performance for instruments measuring aerosol particles

Instruments, such as the diffusion charger (DC), Scanning Mobility Particle Sizer (SMPS) or Electrical Low Pressure Impactor (ELPI) used for sizing and measuring aerosols, modify the electrical charge on particles before detection. Particle charging performance depends greatly on particle diameter and decreases rapidly as particle diameter decreases especially for nanoparticles.
Several papers on the **development or improvement of aerosol charger for sizing instruments** have been published:

- Unipolar charging of nanoparticles by the Surface-discharge Microplasma Aerosol Charger (SMAC) [21]. Kwon S-B et al (2007) report the development and assessment of a unipolar charger for nanoparticles achieving low particle loss and high charging efficiency without the use of sheath air.
- Experimental study of a new corona-based unipolar aerosol charger [22]. Qi et al (2007) have developed and evaluated a corona-based unipolar aerosol charger that provides higher extrinsic charging efficiency than other corona-based unipolar chargers.
- Unipolar field and diffusion charging in the transition regime - Part I: A 2-D Limiting-sphere model [23]. Unipolar field and diffusion charging in the transition regime - Part II: Charging experiments [24]. Marquard A et al (2007) have examined both theoretically and experimentally the application of an additional external field to enhance ion diffusion charging in the transition regime and therefore to allow higher charge levels for nanoparticle aerosols.

An abstract reporting on the improvement of an aerosol charger for electrostatic precipitators has been published:

- An efficient nanoparticle charger. Tsai C-J et al (2007) (Conference abstract) [25]. The authors used four gold wires of 100 μm in diameter as the discharging wires to generate unipolar ions inside the charger. They claimed that for nanoparticles below 10 nm, the

intrinsic charging efficiency of their charger is much higher than those published in the literature. Electrostatic precipitators are filtration devices, which remove particles and their collection efficiency is strongly dependent on the electrical properties of the particles.

Evaluation of instrument for physical and chemical characterisation

In addition to concentration levels of airborne nanoparticles, the physical and chemical characteristics of engineered nanoparticles are important parameters for discrimination against natural ultrafine particles or those produced from combustion. Real-time instruments measuring mass, number, surface area concentrations do not provide chemical or morphological information and it is recognised that in workplaces discrimination between engineered nanoparticles and background sources ultrafines is difficult. However, physical and chemical characterisation techniques such as electron microscopy usually require collection of a sample for off-line analysis.

Three papers reporting the evaluation of devices or the development of methodologies for the collection and characterisation of airborne nanoparticles have been identified.

A thermophoretic precipitator for the representative collection of atmospheric ultrafine particles for microscopic analysis. Lorenzo R et al (2007). [26]

The authors reported on the evaluation and calibration of a plate-to-plate thermophoretic precipitator for the collection of nanoparticles on transmission electron microscopy (TEM) grids. The authors calibrated the instrument using polydisperse (with modes at 45 nm and 90 nm) and monodisperse (with sizes of 40 nm and 80 nm) silver aerosols. The sampling efficiency of the precipitator seems to be independent of the particle size between 15 nm and 300 nm. The particle deposition in the centre of the TEM grid (approximately 1mm in diameter) was homogeneous. On a larger scale, larger variations in the particle deposition efficiency were reported (with higher particle number concentrations at the centre of the grid than near the edge). A numerical model was developed and used to derive a particle number density and size distribution of calibration aerosols. The authors found that: “particle size distributions and particle size number concentrations derived from TEM image analysis combined with deposition coefficients extracted from the author’s model agree very well with the SMPS (Scanning Mobility Particle Sizer) measurements”.

Inertial classification of nanoparticles with fibrous filters. Otani Y et al (2007). [27]

Otani Y et al (2007) assessed the possibility of inertial classification of nanoparticles using a stainless steel fibre filter operating at high filtration velocities. The classification performance was assessed, using a scanning mobility particle sizer, with a polydisperse aersol ($ZnCl_2$) of particle size range between 6 nm and 300 nm. The filter had a thickness of 8 mm with fibres of 8 μm in diameter, a packing density of 0.0065 and a filtration diameter of 4 mm. The authors reported that:

- A 50% cutoff diameter of particles as small as 50 nm at the filtration velocity of 50 m/s could be achieved.
- This inertial filter had a low pressure drop compared to a low pressure impactor.
- The authors also claimed that: “by increasing the filtration area of inertial filter, they can achieve high sampling flow rate to collect particle masses sufficient for chemical analysis”.

Xiong JQ et al (2007) have proposed a combined method for the sampling, quantification and characterisation of airborne carbon nanotubes [28]. The authors reported to use:

- a 13-stage Electrical Low Pressure Impactor (ELPI) for the sampling of airborne nanoparticles and the measurement of number size distributions.
- an Atomic Force Microscope (AFM) for the three dimensional morphological analysis of the particles collected by the ELPI.

Standards and generation of airborne nanoparticles

It is important that the performance and detection limit of instruments used in workplaces for assessing exposure to airborne engineered nanoparticles are investigated. There is a need to generate stable and reproducible well characterised nanoparticle aerosols in the laboratory environment for the calibration and testing of instruments measuring airborne nanoparticles.

A number of abstracts related to the generation of nanoparticle aerosols or provision of reference materials have been submitted to the third International Symposium on Nanotechnology, Occupational and Environmental Health in Taipei (Taiwan, 2007) including:

- The production of large quantities of reference electrostatically stabilised gold and silver nanoparticles by a rapid reproducible sol-phase synthesis method [29].
- The generation of single walled carbon nanotubes (SWCNTs) by electrospraying of nanoparticles suspensions [30]. Ku BK (2007) claimed that SWCNT aerosols with a modal diameter of approximately 20nm can be generated by electrospraying using a selected capillary tube size and buffer composition.
- The generation of single walled carbon nanotubes (CNTs) using a Palas RGB 1000 powder disperser (made of a cylindrical feed stock reservoir and a brush) and a two-component fluidized bed [31].

1.3 Control

Control plays a crucial part in the protection of workers' health. Legislation requires the hazards and risks to be controlled. If it is not practicable to eliminate the risks, then the risks need to be reduced through substitution or engineering controls, the last level of control being the provision of personal protective equipment (PPE).

As observed in the previous bulletins, very few articles on the performance of engineering control for nanoparticles have been published. This current search only identified a peer-reviewed paper on engineering control but a number of studies are currently being undertaken and have been presented at the third International Symposium on Nanotechnology, Occupational and Environmental Health in Taipei (Taiwan, 2007). A number of relevant abstracts on filtration have also been identified.

Engineering control

A paper reporting a device for the engineering control of nanoparticles has been published.

A device for trapping nano-particles formed in processing plasmas for reduction of nano-waste. Iwashita S (2007). [32]

The authors developed and investigated a device for the trapping of airborne nanoparticles formed in low pressure plasmas. This filter device is an assembly of two stainless-steel plates of 0.8 mm in thickness with 19 or 20 slits of 3 mm in width. The capture process works by collision and attachment of particles to the plates. From experimental measurements, the authors claim that: "the filter device has a high trapping efficiency above 99.8% for nanoparticles above 2 nm in size at low ambient pressure (below about 160 Pa)".

Local Exhaust Ventilation (LEV) is widely used to control airborne contaminants. It is important that the effectiveness of LEV systems for nanoparticles are evaluated. Two abstracts considering the effectiveness of LEVs have been published:

Airborne nanoparticle exposures associated with the manual handling of nanoalumina in fume hoods. Tsai S-J (C) et al (**Conference abstract,** 2007) [33]

The authors investigated the potential exposure to airborne nanoparticles during the handling of powders in two chemical laboratory hoods used in the USA university and research laboratories. The handling took place 15 cm from the hood face. The tasks included the transfer of nanoalumina powder from beaker to beaker using a spatula and by pouring action. The abstract report some of the results:

- Increased particle number concentration (up to 13 000 particles/cm^3) were measured, using a fast mobility particle sizer, at the operator breathing zone during handling and post-handling as well as during cleaning.
- More particles were extracted while the hood performed at highest face velocity of 1m/s and the sash was lowered to the operator low chest height.

Capture efficiency of local exhaust hoods for nanoparticles. Lu B-H et al (**Abstract conference**, 2007) [34]

The authors evaluated the effectiveness of a 30m^3 ventilated test cabin using an engine exhaust particle sizer (EEPS). An EEPS is a fast mobility particle sizer. Airborne nanoparticles with diameters of 4-10nm were generated using a spray drying type aerosol generator. The abstract reported that:

- The capture efficiency did not seem to vary significantly as a function of nanoparticles size.
- No significant difference was found between the efficiency measured using SF6 and the nanoparticle aerosol.

A conference abstract (Sachweh B, 2007) mentioned an integrated process strategy based on a direct transfer of the nanoaerosols produced by gas phase flame process into a liquid [35].

Filtration

Filtration is used in diverse control methods such as air cleaning or personal respiratory protection. It is important that filter penetration efficiency is tested for nanoparticle aerosols. A number of abstracts, presented at the third International Symposium on Nanotechnology, Occupational and Environmental Health in Taipei (Taiwan, 2007) and a peer-reviewed paper

have been identified. However no studies on 'face-fit testing' of respirators have been retrieved from this search.

Efficiency of respiratory filters against ultrafine particles. Möhlmann C et al (**Conference abstract**, 2007) [36]

The authors carried out penetration measurements on **a range of filters for respiratory protective equipment**. The penetration characteristics were assessed with airborne salt nanoparticles (median diameter of about 30nm and welding aerosol) by measuring the number concentration before and after the filter. The selected airflows in these experiments (95 and 47.5l/min) depended on the single or twin use of the filters. The abstract reported that:

- Very few particles were measured after the P3 glass filter.
- The P2 electrostatic pad filter showed a better performance than the P2 glass fibre filter. The least efficiency performance was observed at around 60nm for P2 electrostatic filters and 200nm for P2 glass fibre filters.
- In general, an increase in filter efficiency was observed for small nanoparticles (down to 14nm).

In this abstract, the authors gave the following table on the integrated penetration values of a range of filters for the whole size range from 14 to 100 nm:

	Penetration (in terms of number)	Penetration (in terms of mass)	Maximum penetration (EN 143) (in terms of mass, whole size range)
Glass fibre P2	0.654%	1.354%	6%
Glass fibre P3	0.007%	0.018%	0.05%
Electrostatic pad P1	1.477%	2.109%	20%
Electrostatic pad P2	0.290%	0.543%	6%

Penetration of 4.5 nm to 10 µm aerosol particles through fibrous filters. Huanga S-H et al (2007) [37]

The authors have experimentally assessed the penetration of aerosol particles with diameters between 4.5 nm and 10 µm through fibrous filters. Three particle size spectrometers were used to measure nanometer, submicron, and micron-sized particles. NaCl aerosol particles were generated by using spray-drying methods. The authors selected two commercially available filtering facepiece respirators for this study: Respirator A equips with an NIOSH approved N95 class filter, and respirator B has a FFP1 (EN149:2001) mask. The filters were dipped in isopropanol to eliminate electrostatic charges and were allowed to dry. The dipped filters, along with controls of each filter type, were tested. The authors found that:

- The two filters tested were heavily reliant on the electrostatic charge to provide sufficient filtration efficiencies.
- The aerosol penetration values in the 10 nm - 5 µm size range increased noticeably with reducing electrostatic charge on the fibers of the filters and the most penetrating particle size shifted noticeably from the nanometer-sized to sub-micrometer-sized range.
- Almost all particles with sizes below 10 nm and above 5 µm were collected in the filters and t he filter charge density did not significantly affect the penetration values.
- No thermal rebound of particles in the size range down to 4.5 nm in fibrous filters were observed.

Filtration efficiency is usually determined for spherical particles, whereas many particles have non-spherical and nanoparticles tend to form agglomerates. Two abstracts related to the effects of agglomerated fractal-like nanoparticles on the efficiency of filtration have been published:

Bałazy A and Podgórski A (**conference abstract**, 2007) investigated theoretically the deposition efficiency of agglomerates with different fractal dimensions (1.65, 2.05 and 2.50) and different primary nanoparticle sizes (5, 10 and 20nm) [38]. The abstract reported that:

- Small agglomerates have similar deposition efficiencies than spherical particles of the same mobility diameter. Larger agglomerates have different deposition efficiencies than spherical particles of the same mobility diameter.
- The deposition efficiency differs for agglomerates with different fractal dimension.
- Greater difference may be observed between the deposition efficiency of fractal-like agglomerates and spherical particles of the same mass.

Wang J et al (**conference abstract,** 2007) studied the effects of the morphology of nanoparticle agglomerates on the filtration efficiency [39]. Filtration tests were carried out with spherical particles and agglomerated fractal-like silver nanoparticles of different morphologies. A mathematical model for agglomerated particles was also developed. The abstract reported:

- For small mobility diameter (e.g. 50nm), the penetration of agglomerates was similar to that of spherical particles.
- For large mobility diameter (e.g. 300nm), the penetration of agglomerates was considerably lower than of spherical particles.

Aerosol filtration in fibrous filters at nanoscale: nanofibers and nanoparticles. Podgórski A et al (**Conference abstract**, 2007) [40]

The authors produced five nanofibrous media and compared their collection efficiency with microfibre media. It is suggested that nanofibrous media may improve collection efficiency of the most penetrating particles. The abstract reported that:

- A significant increase of the collection efficiency was observed for the nanofibrous media, especially for the most penetrating particles.
- Thermal rebound and thermal re-suspension occurred at particles smaller than 40nm for a polyester filter made of fibres with mean diameter of 24 μm.

Personal protective clothing

Personal protective clothing is used to protect workers from skin contact to chemical substances or dust. It is important that the penetration of clothing materials is tested for nanoparticle aerosols.

Nanoparticles penetration through protective clothing materials. Huang S-H et al (**Conference abstract,** 2007) [41]

Huang investigated the penetration of nanoparticles through protective clothing media. The authors generated neutralised aerosols of polydisperse nanometer, submicrometer and

micrometer size particles. The aerosol concentrations were measured upstream and downstream of the clothing material. The abstract reported that:

- The penetration curve of the protective clothing materials were similar to that of mechanical filter media.
- The most penetrating particle size was in the particle range of ~ 100 to 500 nm (protective clothing (PC) 5 had a penetration of ~ 17% at 100nm compared to protective clothing (PC) 2, which had a penetration of ~ 80% at 500 nm). From the graph in the abstract, PC2 and PC5 showed a penetration of ~ 30% and close to 0% respectively at 4nm and of ~ 75% and ~ 17% at 100nm. It is unclear whether the air flow rate used for the measurement penetration was 10l/min for PC5 and 32l/min for PC2.

It is an interesting study but these results may not be representative of potential penetration during use.

1.4 Characterisation

Characterisation of bulk nanomaterials

Generation of nanoparticles

For inhalation toxicology studies, it is important that reproducible and stable aerosols of defined particle size distribution and concentration are generated over the duration of exposure. This can be highly challenging. A number of papers addressing these issues on the generation of nanoparticles for toxicology studies have been published:

- Gas-phase flame synthesis and characterization of iron oxide nanoparticles for use in a health effects study (Guo B and Kennedy IM, 2007) [42].
- Generation of C60 nanoparticle aerosol in high mass concentrations (Gupta A et al (2007)) [43].
- Generating nanoscale aggregates from colloidal nanoparticles by various aerosol spray techniques (Mahurin SM and Cheng M-D, 2007). This paper discusses the advantages and disadvantages of three generations methods (pressure-driven atomization / nebulization, ultrasonic generation and electrospraying) in relation to toxicology experiments [44].
- Long-term stability characteristics of metal nanoparticle generator using small ceramic heater for inhalation toxicity studies [45].

Dispersion and characterisation of nanoparticles in liquids

It is recognised that complete and accurate particle characterisation is essential for understanding the potential toxicological properties of nanoparticles. Furthermore, characterisation of nanomaterials is fundamental to ensure consistency and reproducibility of any tests.
Several papers have been published on the characterization of nanoparticles in their bulk form, in fluids (biological or water / solvent) or for toxicological evaluation. Microscopy is important for such characterisation. Two interesting papers have been selected for this bulletin:

- Kapp N et al (2007) present two different imaging techniques in transmission electron microscopy (TEM): electron spectroscopic imaging (ESI) and image electron energy-loss

spectroscopy (EELS). These techniques were applied to investigate the distribution of 22 nm titanium dioxide in lung tissue of rats after an inhalation study [46].
- Hell SW reviewed the advances in optical fluorescence microscopy with an emphasis on the breaking of the diffraction barrier and the emergence of far-field optical nanoscopy [47]. The nanoscale 3D imaging of live cells at high speed might be possible in the future. Such technical breakthrough would provide a very useful tool in nanotoxicology.

Nanoparticles tend to agglomerate and clump in solutions. Inadequate dispersion and unsatisfactory characterisation of nanoparticles in liquid for *in vivo* and *in vitro* experiments may lead to inaccurate toxicity assessment. The search identified several papers reporting on dispersion media and techniques to characterise nanoparticle agglomeration in solution, including:

- Improved method to disperse nanoparticles for *in vitro* and *in vivo* investigation of toxicity (Sager TM et al (2007)) [48]. The authors have assessed and compared how various suspension media dispersed nanoparticles using light microscopy and electron microscopy (scanning and transmission electron microscopy (TEM and SEM)). For light microscopy, the samples were placed onto a pre-cleaned micro-slide, were covered and viewed using x10 and x40 objectives. For SEM and TEM, the suspensions were aerosolised at a flow rate of 1ml/min with an atomizer using dry filtered air at 35psi and the samples were collected onto 25 mm polycarbonate filters at a flow rate of 3l/min. The article did not specify the pore size of the polycarbonate filters. This aerosolisation stage may have also changed the characteristics of the agglomerates in these suspensions.

- A comparison of dispersing media for various engineered carbon nanoparticles (Buford MC et al (2007)) [49]. The authors have assessed how various media dispersed carbon nanoparticles using light microscopy. The suspensions were pipetted onto a microscope slide, covered-slipped and imaged at 400 times magnification under white light.

- Visualization and dynamic size evaluation of nanoparticles in solution by single optical fiber-illuminated microscope analysis (Suzuto M et al (2007)) [50]. The authors have reported on an optical microscopy method using an optical fibre laser as the light source. Particles in real time and in liquids are visualized and the paths of the particles under Brownian motion are tracked and analysed over a period of time. An instrument manufactured by Nanosight Ltd (UK) with a similar configuration to the one presented in this paper is commercially available.

1.5 Bibliography of key papers

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2. HEALTH EFFECTS

The publications retrieved by the health effects searches in the four months from July to October 2007 showed a similar pattern of distribution amongst the different topics to previous bulletins. Many of the primary publications described effects of engineered nanoparticles in *in vitro* systems (Figure 2), almost equal numbers of papers describing effects of nanoparticles on human cells (12%) and animal cells (15%) grown *in vitro*. The proportion of publications (19%) describing the effects of engineered nanoparticles in animals was very similar to previous bulletins. A large number of reviews (40%) was retrieved by the health effects searches for the period July to October 2007.

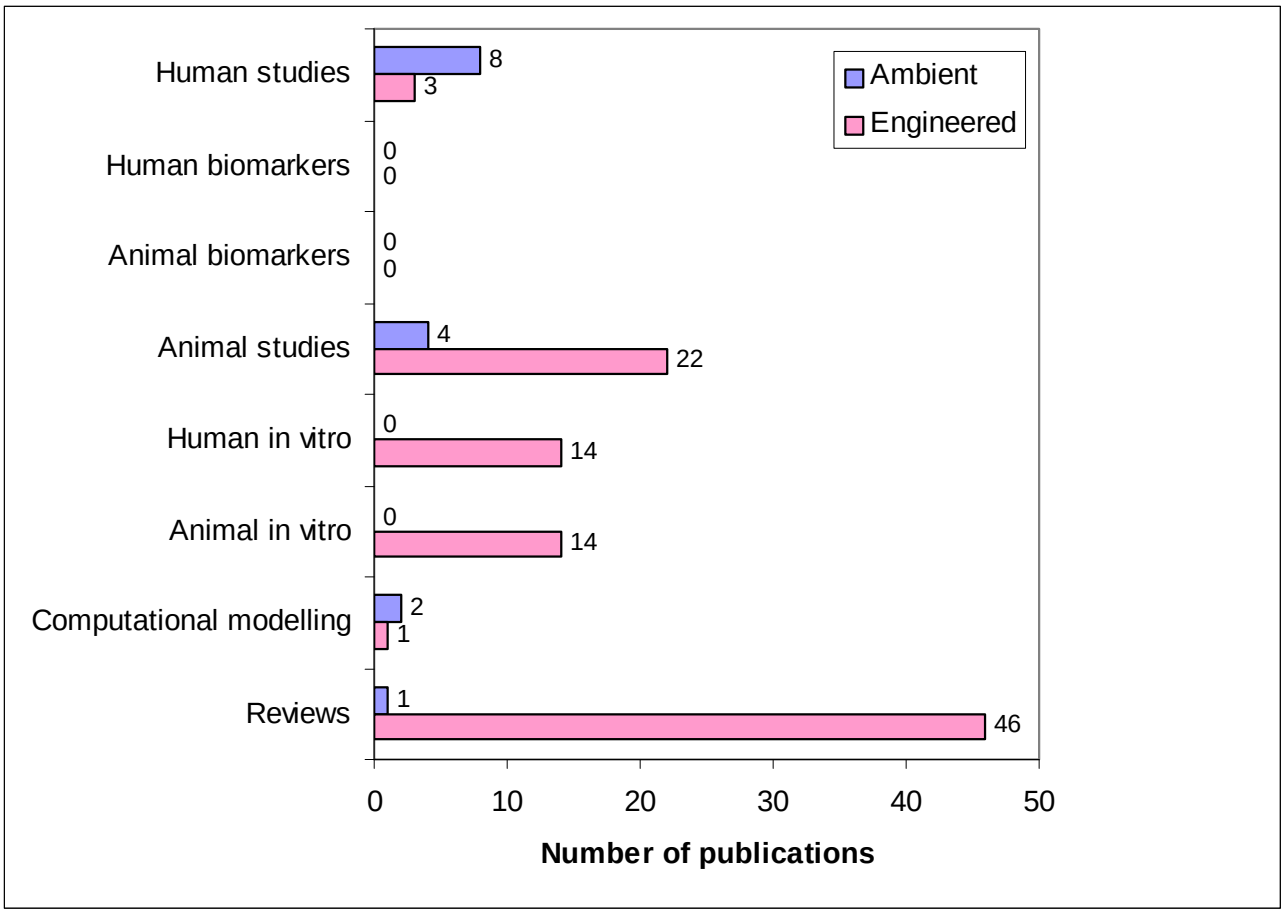

Figure 2: Breakdown per topic of the numbers of publications retrieved in the four months from July to October 2007 on the human health effects of *ambient* and *engineered* nanoparticles.

2.1 Human studies and epidemiology

The searches retrieved three studies of the potential human health effects of engineered nanoparticles. Two of these build on previous studies of the occupational effects of carbon black (CB), which have shown that although standard mortality ratios (SMR) are increased for CB workers, they do not correlate with likely exposures (Issue 2, May 2007).

A "lugged" analysis of lung cancer risks in UK carbon black production workers, 1951-2004. Sorahan & Harrington (2007) [1]

A novel approach was taken to analyse the lung cancer risk in a cohort of 1,147 male workers who were employed for at least 12 months in one of five UK factories manufacturing CB. Work histories in the last 15 years were considered (referred to as a "lugged" analysis, in contrast to conventional lagged analysis, which considers exposure occurring more than 15 years ago). Significantly increased SMRs were seen for lung cancer at two of the plants. However, elevated lung cancer risks were limited to workers employed in the most recent 15 years, and there was a positive relationship between lung cancer risk and cumulative CB exposure (mg/m^3/year) within that time period. **The authors conclude that exposure to CB (or chemicals associated with its production) may have an effect on the *later* stages of lung carcinogenesis, which translates into the SMR decreasing with time since employment when exposure ceased. However similar "lugged" studies on other CB cohorts are needed to corroborate these findings.**

To explore further the hypothesis of Sorahan and Harrington, Morfeld and McCunney carried out a similar analysis of a German cohort of CB workers:

Carbon black and lung cancer: testing a new exposure metric in a German cohort. Morfeld & McCunney (2007) [2]

The methods of Sorahan and Harrington [1] were used to analyse a German cohort of 1,528 CB workers (1,271 workers at inception), focusing on the first 15 years since hire and since leaving employment. The results differed from the UK cohort study: the lung cancer SMR increased with time since exposure ceased in both the full and inception cohorts. **The authors conclude that this preliminary study does not support the hypothesis of Sorahan and Harrington [1], since there was no decrease in lung cancer risk with time since employment / exposure ceased.**

The third study examined the safety of nanocrystalline silver dressings in 30 burns patients [3]. Although the clinical emphasis of this paper makes it less relevant for this bulletin, it is included since the authors report that silver was absorbed (median time to maximum silver levels was 9 days; median maximum serum level of silver was 57 μg/l and median serum level after 6 months was 0.8 μg/l), but no haematological or biochemical indicators of toxicity were noted.

The remaining eight publications examined the effects on human health of ambient particles (ultrafine and fine), and are therefore of lower priority for this bulletin. One paper examined the effects of ultrafine particles, of defined sizes, from vehicle exhaust on DNA damage in healthy adults:

Exposure to ultrafine particles from ambient air and oxidative stress-induced DNA damage. Brauner et al (2007) [4]

Oxidative DNA damage and repair were studied in peripheral blood mononuclear cells (PBMCs) in 29 healthy adults during controlled exposure to urban air particles with diameters of 12, 23, 57 or 212 nm. Exposure for 6 or 24 hours dose-dependently increased the levels of DNA strand breaks and oxidized purines (as formamidopyrimidine DNA glycolase sites), with the 57 nm particles having the greatest effects. Exercise for 3 hours had no significant

effect. Activity of 7,8-dihydro-8-oxoguanine-DNA glycolase (OGG1), or expression of OGG1, nucleoside diphosphate linked moiety X-type motif 1 (NUDT1) or heme-oxygenase-1 were unaltered. **The authors conclude that ultrafine particles from vehicle emissions can cause systemic oxidative DNA damage, with no compensatory increase in DNA repair within 24 hours.**

Three papers considered the effects of air pollution ($PM_{2.5}$) on children's health and infant birth-weight [5-7]. A fourth paper reviewed the potential relationship between indoor airborne ultrafine particles and childhood asthma, suggesting that further research in this area is required [8]. Two studies investigated the inflammatory effects of air pollution on cardiac patients: increases in interleukin-6 and fibrinogen (but not C-reactive protein) occurred in myocardial infarction patients in response to elevated ambient particle number concentrations [9], and in the second study, coronary artery disease patients showed repolarisation changes (in ECG recordings) and increased plasma von Willebrand factor and C-reactive protein levels in response to traffic-related ultrafine and combustion-generated particles [10]. The final study in this category was a meta-analysis in which the spatial extent of impact for mobile sources of different air pollutants (including ultrafine particles) was investigated, and reported to be 100-300 metres for ultrafine particles [11].

2.2 Animal *in vivo* studies

The key routes for potential human exposure to nanoparticles are inhalation and dermal contact. No publications were identified in the health effects searches that reported effects of dermal exposure to engineered nanoparticles in animals. However sixteen publications reported the effects of pulmonary administration of engineered nanoparticles in animals. Five of these considered carbon fullerenes or nanotubes (CNTs), which are thought to be of potentially high concern:

Engineered carbon nanoparticles alter macrophage immune function and initiate airway hyper-responsiveness in the BALB/c mouse model. Hamilton et al (2007) [12]

The effects of three types of carbon nanoparticles (single walled and multi-walled nanotubes and C60 fullerenes) were investigated *in vivo* by intranasal instillation into mice and *in vitro* using mouse alveolar macrophages. In mice, the carbon nanoparticles were pro-inflammatory, exacerbating airway hyper-responsiveness and leading to macrophage influx into the lungs. *In vitro*, the nanoparticles modulated immune function of alveolar macrophages and disrupted lipid rafts in the cellular membranes.

Assessing the pulmonary toxicity of single-walled carbon nanohorns. Lynch et al (2007) [13]

Carbon nanohorns resemble carbon nanotubes (CNTs), having a similar carbon atomic structure, but a closed, horn-like shape. Single-walled carbon nanohorns (30 μg) were administered to mice by pharyngeal aspiration, and after 24 hours or 7 days, the bronchoalveolar lavage fluid was analysed. A mild, transient inflammatory response was induced, but no granulomas or fibrotic lesions were noted in the lungs. Microarray analysis revealed no marked changes in gene expression. **The authors therefore conclude that the single-walled carbon nanohorns have low pulmonary toxicity.**

Vitamin E deficiency enhances pulmonary inflammatory response and oxidative stress induced by single-walled carbon nanotubes in C57BL/6 mice. Shvedova et al (2007) [14]

Previous studies from this group have demonstrated that administration of single-walled carbon nanotubes (SWCNTs) induce pulmonary inflammation and early fibrosis, accompanied by oxidative stress and depletion of antioxidants. In the present study, the group has extended these results and shown that in mice, a vitamin E-deficient diet reduces levels of antioxidants in lung tissue, and increases the sensitivity to acute inflammation induced by SWCNTs. Specifically, there were increases in the number of inflammatory cells, levels of LDH, pro-inflammatory cytokines (interleukin-6 (IL-6) and tumour necrosis factor (TNF-α)), and in the fibrotic response (transforming growth factor-β and collagen) compared to mice fed a vitamin E-sufficient diet. **The authors conclude that vitamin E deficiency enhances SWCNT-induced pulmonary inflammation, and they suggest that the results may have practical implications in terms of protective strategies.**

Enhanced peripheral thrombogenicity after lung inflammation is mediated by platelet-leukocyte activation: role of P-selectin. Nemmar et al (2007) [15]

The systemic prothrombotic effects of intratracheal instillation of multi-walled ground CNTs were investigated in Swiss mice. A number of effects were observed in the treated not control mice:

- Neutrophil (not macrophage) influx into the lungs 24 hours after instillation.
- Early (6 hours) but transient activation of platelets (measured by platelet-leukocyte conjugate formation).
- Increased plasma pro-coagulant tissue factor (TF) activity after 24 hours.
- Longer bleeding times but enhanced peripheral thrombogenicity.
- Neutralisation of P-selectin inhibited the platelet-leukocyte conjugate formation, TF generation and increased thrombogenicity.

The authors conclude that CNT-induced lung inflammation leads to activation of platelets and P-selectin-mediated systemic inflammation, accompanied by leukocyte activation and increased procoagulant risk.

Comparative pulmonary toxicity assessments of C60 water suspensions in rats: few differences in fullerene toxicity *in vivo* in contrast to *in vitro* profiles. Sayes et al (2007) [16]

The aim of this work was to investigate whether the differences in toxicity between aggregated, underivatised fullerenes ("nano-C60") and fully derivatised, water soluble fullerenes observed *in vitro* translate into similar effects following pulmonary instillation in rats. The lungs of the animals were analysed 1 day, 1 week, 1 and 3 months after administration of 0.2-3.0 mg/kg fullerenes, by bronchoalveolar lavage (BAL) and histopathological examination. Both fullerenes induced transient inflammation, cell injury effects and lipid peroxidation. **The authors conclude that these results do not corroborate differences in toxicity seen between the fullerenes *in vitro* and highlight the problems of extrapolating *in vitro* results to *in vivo*.**

A further study compared inflammatory effects *in vivo* and *in vitro* of nanoparticles following instillation:

Proinflammogenic effects of low-toxicity and metal nanoparticles *in vivo* and *in vitro*: highlighting the role of particle surface area and reactivity. Duffin et al (2007) [17]

The pulmonary inflammatory response to instillation of low toxicity dusts of different particle sizes is a function of the dose expressed as surface area rather than mass. To explore whether this approach can be used to assess the reactivity of highly toxic dusts, DQ12 quartz or DQ12 treated with aluminium lactate was instilled into rats. DQ12 quartz induced a significantly larger inflammatory response than would be predicted on the basis of surface

area alone, owing to its surface reactivity, whilst the response to DQ12 treated with aluminium lactate was similar to low toxicity dusts. The response to the nanoparticles in the respiratory cell line A549 *in vitro* also reflected surface area and reactivity.

Two studies have investigated effects of carbon black in rodents:

Nano-sized carbon black exposure exacerbates atherosclerosis in LDL-receptor knockout mice. Niwa et al (2007) [18]

To investigate whether long-term exposure to nano-sized CB exacerbates atherosclerotic lesions, LDL-receptor knockout mice were fed a 0% or 0.51% cholesterol diet and given an intratracheal dispersion of CB (1 mg/week for 10 weeks). Aortic lipid-rich lesions were only observed in mice fed the cholesterol diet (with or without CB), and the CB treated mice had significantly larger lesions than the control mice. **The authors conclude that exposure to CB can accelerate development of atherosclerosis.**

Interaction effects of ultrafine carbon black with iron and nickel on heart rate variability in spontaneously hypertensive rats. Chang et al (2007) [19]

To test the hypothesis that different components of particulate matter have different effects on heart rate variability, 14 nm CB, $Fe_2(SO_4)_3$ or Ni SO_4 alone or in combination were intratracheally instilled into spontaneously hypertensive rats and radiotelemetry data were collected for 72 hours. The different particles induced different responses when given alone or together. **The authors conclude that different particles can induce different responses in different cardiac phases, which may interact during concurrent exposures.**

Of the other eight studies that have administered engineered nanoparticles via an inhalation route, two papers reported the effects of silver or titanium dioxide nanoparticles respectively, which are being used increasingly in a variety of consumer products:

Twenty-eight day inhalation toxicity study in Sprague-Dawley rats. Ji et al (2007) [20]

A small ceramic heater was used to generate silver nanoparticles, which were sized and counted using a differential mobility analyser and condensation particle counter. Rats were exposed to fresh air, low (17,300/cm^3), medium (127,000/cm^3) or high (1,320,000/cm^3 = 61 $\mu g/m^3$) doses of silver nanoparticles for 6 hours/day, 5 days/week for 4 weeks. There were no significant changes in body weight, haematology or blood biochemistry. **The authors conclude that inhalation of silver nanoparticles at concentrations close to the ACGIH silver dust limit of 100 $\mu g/m^3$ was not associated with any apparent health effects.**

Inflammatory response of mice to manufactured titanium dioxide nanoparticles: comparison of size effects through different exposure routes. Grassian et al (2007) [21]

Mice were acutely exposed to titanium dioxide nanoparticles (5 and 21 nm) either by whole body exposure or nasal instillation. The administered nanoparticles were characterized in the aerosol and instillation solution. The endpoints assessed included histopathological examination of the lungs, and analysis of BAL fluid: cell counts, total protein, LDH and cytokine content. The larger nanoparticles were found to be more toxic. **The authors conclude that the agglomeration state of the nanoparticles may be as important as surface and physical properties in determining their toxicity.**

A further paper on inhalation of engineered nanoparticles examined the translocation of gold nanoparticles following inhalation:

Translocation and effects of gold nanoparticles after inhalation exposure in rats. Yu et al (2007) [22]

Rats were exposed to $2.10^6/cm^3$ gold nanoparticles (30 or 110 nm) for 5 days. The tissue content of gold was then analysed by ICP-MS. The level of gold in the olfactory bulb and lung increased after 5 days, and with longer exposure (15 days), increases were observed in the lung, oesophagus, tongue, kidney, aorta, spleen, septum, heart and blood. Gene expression and lipid changes were noted in the treated lung, suggesting there is potential for the nanoparticles to have effects in distal tissues.

In preparation for a comprehensive program of inhalation toxicity testing of a range of nanoparticles, BASF has extensively characterized the particles behaviour in an exposure system following generation using a dry particle aerosol generator or by nebulising particle suspensions [23]. The particles in the aerosols were in the respirable size range, but there was considerable agglomeration, such that only a few *mass* percent existed as single particles. However these particles represented a significant number percent. The authors propose a technical set-up and testing approach for their forthcoming inhalation studies.

The nature of the vehicle in which nanoparticles are suspended for inhalation as well as other routes of administration can significantly affect the degree of agglomeration; Buford et al dispersed carbon nanoparticles in a range of different buffers, noting that the presence of lipid and/or protein led to fewer agglomerates than vehicles without either, and when instilled into mouse lungs, particles in vehicle with serum distributed uniformly in the lungs, with no apparent clearance even after 7 days [24]. Further analysis of nanoparticle dispersion methods for either animal or *in vitro* experiments has utilised light and electron microscopy [25]; dispersion of nano-sized and larger carbon black and titanium dioxide particles was best in BAL fluid, compared with PBS with or without protein or lipid. These results are not only informative for experimental dispersal of nanoparticles, but may have implications for interactions between inhaled particles and BAL *in vivo*.

A particular challenge for *in vivo* (and *in vitro*) experiments is localization of nanoparticles following delivery. Following a paper highlighted in the last bulletin (Issue 3, July 2007), a new paper considers different electron microscopy techniques for evaluating changes in the lung and nanoparticle distributions following inhalation, drawing attention to the possibility of using light and electron microscopy in a correlative approach [26].

Six studies of the effects of engineered nanoparticles administered *in vivo* by other routes were retrieved by the searches. The first paper assessed the acute toxicity (in terms of liver and kidney functions, and blood biochemistry) at different time points up to 14 days after intravenous injection of carbon-coated iron nanocrystals in mice [27]. The median lethal dose or LD_{50} was 203.8 mg/kg, with only mild changes seen at 80 mg/kg. Two publications considered quantum dots (QD), autofluorescent, semi-conductor nanocrystals with a wide range of applications. One paper reported that the QD surface coating material influences both their biological effects and cytotoxicity [28], although it is unclear from the abstract whether the experiments were conducted *in vivo* or *in vitro*. The second paper investigated the tissue kinetics of QD in mice:

Persistent tissue kinetics and redistribution of nanoparticles, quantum dot 705, in mice: ICP-MS quantitative assessment. Yang et al (2007) [29]

The blood and tissue kinetics of QD705 were quantified in mice for up to 14 days after a single intravenous injection (40 pmol). Inductively coupled mass spectrometry (ICP-MS) of cadmium and fluorescence microscopy showed that although the plasma half-life was short (18.5 hours), the QD continued to accumulate in tissues, specifically the liver, kidney and spleen. No excretion via faeces or urine was detected. **The authors conclude that QD has a long tissue half-life, persisting potentially for weeks or months.**

A further study investigated the tissue distribution of gold nanoparticles, reporting very different kinetics to those of the QDs:

Kupffer cells are central in the removal of nanoparticles from the organism. Sadauskas et al (2007) [30]

Gold nanoparticles (2 and 40 nm) were injected into female mice intravenously or intraperitoneally, and traced by autometallography after 1, 4 or 24 hours. The nanoparticles were taken up by endocytosis, primarily into the Kupffer cells of the liver and to a lesser extent by other macrophages, in spleen, mesenteric lymph nodes and small intestine, depending on the route of administration. **The authors conclude that gold nanoparticles are taken up primarily by liver Kupffer cells; particles were not found in kidneys, lungs, adrenals, or ovaries, and they did not cross the blood-brain or placental barriers.**

Fetuin may be one of the serum proteins involved in hepatic uptake of nanoparticles (specifically, negatively charged 50 nm polystyrene nanoparticles) by scavenger receptors on Kupffer cells [31].

The final paper that has investigated the potential health effects of engineered nanoparticles in animal studies has shown that nano-sized elemental selenium is an equally effective anti-oxidant but much less toxic in mice (in terms of median lethal dose, acute liver injury, survival rate and short-term toxicity) than Se-methylselenocysteine [32], confirming previous work from this group reported in the third bulletin (Issue 3, July 2007).

A further four publications were identified in the searches that considered the potential health effects of ambient rather than engineered nanoparticles and will only be summarized as these studies are of lower priority for this bulletin. Chang and coworkers showed that dust storm particles (316 mg/m^3 $PM_{2.5}$) induced adverse cardiovascular effects in spontaneously hypertensive rats [33], similarly to diesel exhaust particles (DEPs), which exacerbate lung inflammation caused by bacterial lipopolysaccharide in mice [34]. A further study has shown by proteomic analysis of BAL fluid from rats that specific inflammatory proteins can be identified as part of the acute response to exposure to DEPs [35]. The fourth publication reported that DEPs have adverse effects on spermatogenesis in mice offspring [36]; similar reproductive effects have been reported for engineered nanoparticles (Issue 2, May 2007).

2.3 *In vitro* studies

Of the 30 publications identified in this area by the human health effects searches, 14 reported the effects of engineered nanoparticles in human cells *in vitro*, and will be considered first, since they are considered to be of higher priority for this bulletin than studies in animal cells *in vitro*.

The first paper investigated the potential toxicity of Envirox™, a diesel fuel additive containing nanoparticles of cerium oxide. This paper is considered in detail since the authors used validated, accepted *in vitro* methods:

Initial *in vitro* screening approach to investigate the potential health and environmental hazards of Envirox™ - a nanoparticulate cerium oxide diesel fuel additive. Park et al (2007) [37]

Envirox™, a nanoparticulate cerium oxide catalyst, modifies combustion of diesel fuel and reduces particulate emissions in engine exhaust. A preliminary safety assessment compared nano (9 nm) with non-nano-sized (320 nm) cerium oxide (EINECS # 234-374-3), which is generally regarded as non-hazardous to health:

- In the Epiderm human skin irritation test, neither particle was irritating to skin (although negative results in this test should be confirmed according to OECD TG 404).
- In the BS EN ISO 10993-5 cytotoxicity test, both particles scored 0.

- Both particles were negative in the Ames test for mutagenicity in *Salmonella* with or without metabolic activation.
- Both particles showed no toxicity towards *Daphnia magna* (NOEC or no observed effect concentration was 100%) and had no effect on respiration of activated sewage sludge bacteria (NOEC 1000 mg/l).

The authors conclude therefore that nano-sized cerium oxide does not raise any significant concerns about potential human health effects, and there are no differences compared to the non-nano-sized form.

A second paper using primary animal tissue *in vitro* also considered the toxicity of Envirox™:

Evaluation of cerium oxide and cerium oxide based fuel additive on organotypic cultures of lung slices. Fall et al (2007) [38]

A novel dynamic organotypic culture of precision-cut rat lung slices was used to evaluate and compare the effects on *ex vivo* rat lung tissue of nano-cerium oxide either alone or in diesel fuel at the proposed final concentration of 5 ppm,. This model system is representative of peripheral lung tissue, and has the advantage over *in vitro* isolated cell systems of maintaining the combinations and interactions of all the cell types normally present in lung. A range of cellular endpoints was assessed: changes in intracellular ATP or glutathione S-transferase (GSH), release of tumour necrosis factor (TNF) α, and anti-oxidant activity (glutathione peroxidase, catalase, superoxide dismutase or SOD).

In response to incubation with low ($0.35.10^6$ particles/cm^3), medium ($1.98.10^6$ particles/cm^3) or high ($4.38.10^6$ particles/cm^3) doses of nano-cerium oxide, the only significant changes were increases in catalase activity compared to treatment with air. In response to low (2%), medium (10%) or high (20%) levels of emissions from an engine using diesel without Envirox™, dose-dependent decreases (compared to air) were noted in ATP, GSH and TNFα. When the engine ran on diesel with Envirox™, a decrease in GSH, a small decrease in TNFα and a significant increase in catalase activity (compared to air) were observed. **The authors conclude that the nano-sized cerium oxide used in these studies did not induce any changes in inflammatory markers nor any signs of toxicity in the lung slices, and therefore this diesel additive seems well-tolerated by lung tissue.**

The debate about skin penetration of nanoparticles continues: interactions between QDs and human primary skin cells (NHEK) have been shown to be sensitive to the coating of the QDs, the ambient temperature and media supplements [39].

One paper has examined the phototoxicity of a C60 fullerene dimalonic acid derivative in human HeLa cells, using laser-scanning confocal microscopy to analyse the integrity of cellular membranes, and calcium influx [40]. Irradiation induced damage to plasma and mitochondrial membranes, preceded by transient calcium influx into the cells, suggesting that these events may precede cytotoxicity. Early events following ultraviolet activation of nano-sized titanium oxide have been examined in human skin fibroblasts; exposure of cells to 4 μg/ml TiO_2 with low intensity UV illumination induced a decrease in cellular stiffness, observed by atomic force spectroscopy, suggesting that the photoactivated TiO_2 nanoparticles damage cellular and sub-cellular structures [41]. Four other papers have examined the potential health effects of metal nanoparticles *in vitro*. Gold, copper, iron and CdS nanoparticles have a prothrombotic effect on human platelets, inducing aggregation, by a mechanism that depends on the type of agonist (ADP not epinephrine) and potentially involves the low affinity ADP receptor P2Y21 [42]. In the second paper, the inflammatory effects of nano- and micron-sized particles (oxides of aluminium, cerium, iron III, nickel, silicon and titanium) on human lung BEAS-2B cells were compared with naturally-occurring soil dust particles [43]; the engineered nanoparticles were less potent inducers of interleukins(IL)-6 and –8 than micron-sized particles of similar composition or $PM_{2.5}$ particles from soil dust (on a mass dosemetric), although problems were encountered with

nanoparticles binding to IL-6. The third paper reports the toxic effects of copper oxide nanoparticles in human H4 neuroglioma cells based on quantitative cellular image analysis classifying nuclei into bright, dark and background [44]. The analysis agreed with the previously observed dose-dependent toxic response of the cells to copper oxide nanoparticles. An abstract for a fourth publication in this area was unavailable [45].

Five papers were retrieved in the searches that examined uptake of nanoparticles into human cells *in vitro*, two exploring uptake into respiratory tract cells. A co-culture model consisting of epithelial cells, macrophages and dendritic cells was used to compare the translocation, localisation and cellular responses to particles of different sizes and composition [46]. Translocation was size-dependent, whilst intracellular localisation varied with particle composition (TiO_2 particles of 20-30 nm were found as single particles and in membrane-bound agglomerates, whilst gold particles of 25 nm existed only as single particles). The cellular response varied with both size and composition: polystyrene (1 μm) and gold nanoparticles induced TNF-α, whilst polystyrene and TiO_2 nanoparticles did not. Uptake of TiO_2 nanoparticles into membrane-bound aggregates was also demonstrated in A549 human lung epithelial cells, and despite aggregation, the nanoparticles still induced greater oxidative stress and IL-8 release than larger particles [47]. Uptake of silica nanoparticles was both cell type and charge dependent [48]: positive charge enhanced uptake into mouse 3T3-L1 fibroblasts more than into human mesenchymal stem cells (MSCs), but uptake in both cell types involved clathrin- and actin-dependent endocytosis. There were no effects on viability, proliferation or differentiation. Similarly, neutravidin-conjugated silica nanobeads, functionalised with anti-human CD3 and CD28 antibodies were readily taken into both lysosomes and the cytoplasm of human Jurkat T cells by endocytosis, without apparent cytotoxic effects [49]. The abstract was not available for the fifth paper on nanoparticles uptake into human cells *in vitro* [50].

The effect of charge on cellular effects of nanoparticles has also been studied in the human gut cell line, Caco-2 [51]. Cationic chitosan-N-acetylcysteine nanoparticles caused more severe cytotoxicity than neutral and anionic particles, as well as red blood cell agglutination.

Fourteen papers examined the potential effects of engineered nanoparticles using animal cells *in vitro*; one paper on Envirox™ [38] has already been considered. Two papers describe gene expression changes associated with exposure of BALB-3T3 fibroblasts to cobalt nanoparticles, the authors suggesting that some of the genes/proteins could be explored as potential biomarkers of nanoparticle toxicity [52; 53]. There has also been a report that SWCNTs can deliver electrical signals to hippocampal neurones [54].

Continuing the theme of investigation of nanoparticle uptake into cells, seven publications examined movement of nanoparticles into animal cells grown *in vitro*. Two papers studied interactions between nanoparticles and cell membranes, the first reporting that polycationic organic nanoparticles can disrupt both artificial and living cell membranes [55], and the second that gold nanoparticles (7, 10 and 15 nm) can not cross artificial membranes by passive Brownian diffusion [56]. However, antibody-conjugated QDs are internalised into cells, where they persist for several cell divisions without causing toxicity [57]. The macrophage scavenger receptor, MARCO (macrophage receptor with collagenous structure), appears to be at least partly responsible for cellular endocytosis of polystyrene particles of 20 nm to 1 μm in size [58]. Uptake and the effects of particles in cells can be influenced by protein adsorption onto the particles' surface. Albumin is reported to be the major human plasma protein that adsorbs to SWCNTs, and the resulting conjugates have anti-inflammatory effects in the mouse macrophage cell line, RAW 264.7, inhibiting induction of cyclo-oxygenase (COX)-2 by bacterial lipopolysaccharide (LPS) [59]. This response also depends on scavenger receptors and is inhibited by non-ionic surfactants. Different proteins however adsorbed to silica nanoparticles, and the surfactant reduced both adsorption and

toxicity [59]. Nanoparticle uptake into cells can be followed by flow cytometric side scatter of light, as demonstrated with titanium dioxide, silver and iron oxide particles, ranging in size from 5 nm to 5 μm [60]. Formulas have been proposed to allow design of nanoparticles with controlled endocytotic performance [61].

A number of methods are available for characterising the proteins which adsorb to nanoparticles [62; 63], and it has been shown that on mercaptoundecanoic-stabilised gold nanoparticles, proteins such as albumin, myoglobin and cytochrome c both irreversibly and reversibly adsorb, the adsorption characteristics varying with different proteins [64].

2.4 Computational modelling

Three publications were retrieved by the health effects searches that modelled lung deposition of nanoparticles. Two considered deposition from indoor or outdoor ambient air pollution: Mitsakou et al used a mechanistic model, incorporating aerosol and inhalation dynamics, to calculate the internal dose in different lung regions in different exposure scenarios [65], whilst Molitor et al reported that introducing spatial autocorrelation error terms into models of urban ambient particle exposure improved prediction of adverse health effects [66]. The third paper determined deposition of nanoparticles in different regions of the respiratory tract using a mathematical model of transport by airflow convection, axial diffusion and convective mixing, and found that particles of more than 10 nm deposited primarily in the pulmonary region, whilst smaller particles did not penetrate deeper than the tracheobronchial region [67]. The predictions with this model were reported to correlate well with data in the literature.

2.5 Reviews

A large number of reviews were identified in the human health searches (47), an increase on each of the previous bulletins (Issues 1-3). One review considered potential health surveillance screening strategies that might be used in workplaces where nanoparticles are handled, and concluded that although there are currently no nano-specific strategies, general medical screening has considerable value, since it can inform future epidemiological studies [68].

Announcements of nanotechnology policy initiatives [69], risk assessment guides and frameworks [70; 71], and the inventory status of nanomaterials under the US Toxic Substances Control Act (TSCA) [72] have been made recently. A framework has been proposed for dividing nanoparticles into categories, based on linking their physical and chemical properties to adverse health effects [73], but after analysing a database of published papers, the authors conclude that too few papers report sufficient physicochemical data on the nanoparticles, so that it is not possible to link these to effects observed. A proactive stance is advocated for Australia's regulatory approach to nanomaterials [74], and it is suggested that the European incremental approach to regulation of nanomaterials may require adaptation [75].

There were six general reviews of the potential hazards and risks of nanotechnology [76-83], three focussing on potential human health effects [84-86] and one summarising the first Nobel mini-symposium on nanotoxicology [87]. The relationship between respiratory diseases and ambient air pollution was considered by [88], and nanoparticles more specifically by [89; 90], and a third, a meeting report, discussed the effects of different types of inhaled particles (including nanoparticles) on lung and cardiovascular diseases [91]. A further review asked whether there are available data to support the hypothesis that nanoparticles are male reproductive toxicants, concluding that the particles can cross into and deposit in the testes, and may have adverse effects on sperm [92]. Specific health effects associated with individual nanoparticles were assessed in several reviews: fullerenes

[93] and carbon nanotubes [94-97], with one review focussing on the implications of carbon nanotubes in neuroscience [98], and noting that as reported by [54], CNTs may modify neuronal function. Reviews of quantum dots and apatite nanoparticles were also retrieved by the searches [99; 100]. There were two reviews of potential mechanisms of action of nanoparticles in cells and tissues [101; 102]. Conflicting results obtained in nanotoxicology are assessed by [103].

Continuing discussion in the field of nanotoxicology focuses on the most appropriate dose-metric to use, and Wittmaack has reviewed published data on acute lung inflammation in rodents after instillation of titanium dioxide or carbon nanoparticles, exploring the impact of using different dosemetrics [104]. Although particle number was the best, he concludes that methods to characterise particles and their surface toxicity require refinement before the optimum dosemetric for lung inflammation can be safely determined.

Finally, ten reviews discussed the societal and ethical implications of nanotechnology [105-114].

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