Health & Safety Executive NanoAlert Service

Prepared by the

Health & Safety Laboratory, Buxton, UK

Bulletin Contents:

1. MEASUREMENT, EXPOSURE AND CONTROL

In this bulletin, 113 papers were identified and abstracts were reviewed. 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.

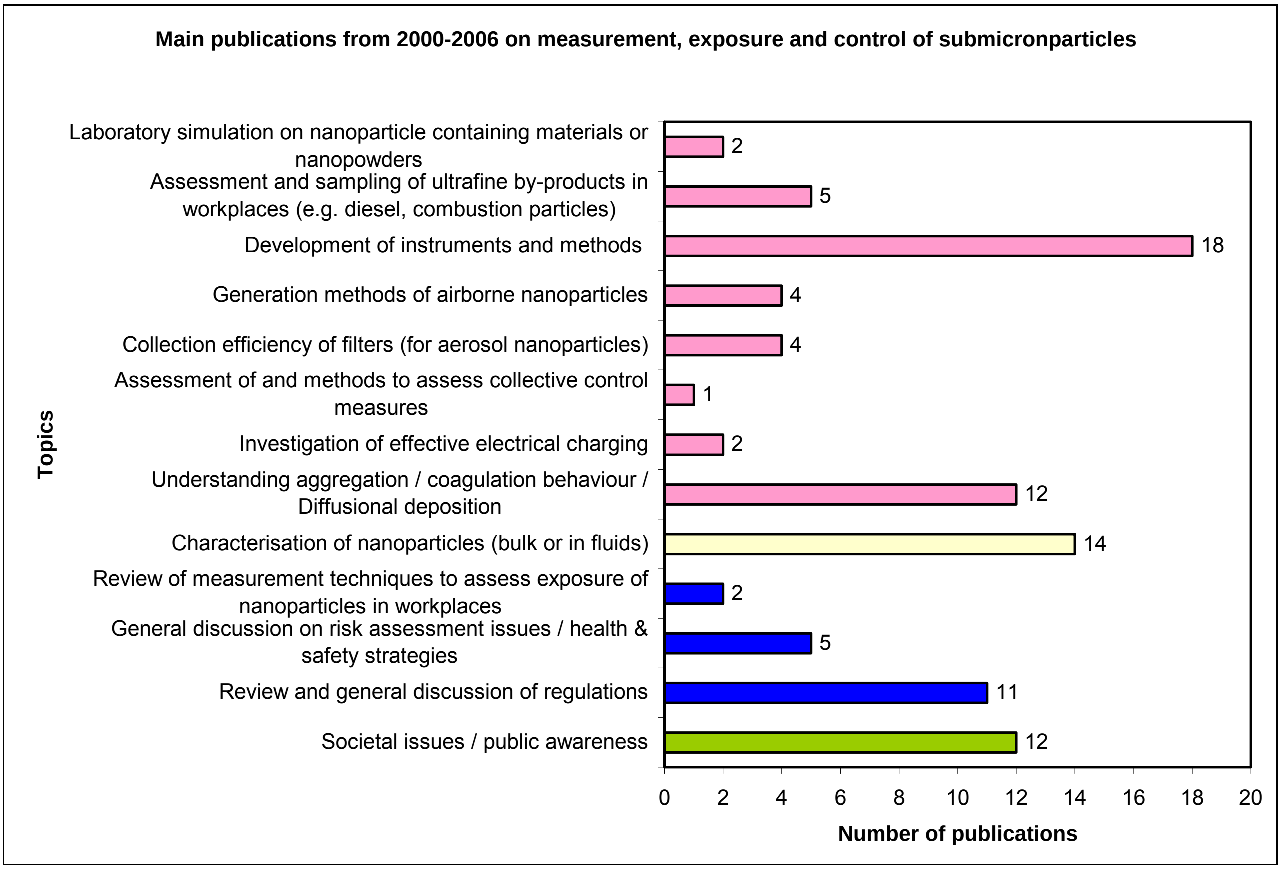

Figure 1: Breakdown of the number of papers per topic (measurement, exposure and control)

- The search did not identify any studies reporting exposure measurement of nanoparticles in workplaces.
- The search retrieved two papers reporting laboratory simulation on nanoparticle containing materials or nanopowders:
    - Investigation on behaviour of carbon black and amorphous silica during mechanical processes.
    - Evaluation of nanoparticles emission from TiO2 nanopowder coating materials in a simulated box.

- The search identified 18 papers on development of instruments and methods to measure exposure to nanoparticles / ultrafines. Sixteen papers mainly focussed on current instruments or methods for measurement of airborne nanoparticles or ultrafines including investigation of performance and calibration of such instruments. Two of these papers looked at biological sampling methods or strategies. In addition, four papers on generation methods of airborne nanoparticles (such as metal nanoparticles), which may be useful for the calibration of instruments or validation of methods, have been found.

- The search did not identify any papers reporting data on the effectiveness of control measures to reduce exposure to engineered nanoparticles. However, a paper investigating reduction of welding nanoparticles by modification of the ventilation system has been published. Four papers on collection efficiency of filters have also been identified.
- The search found approximately 20 papers on the use of instruments / methods to assess exposure of airborne environmental ultrafine particles (e.g. diesel particles).
- The search also identified a number of reviews or general articles (28) on regulations (11), risk assessment (5) and societal issues / public awareness (12).

1.1 Exposure data

Workplace exposure

This current search did not identify studies on workplace exposure or dispersion of nanoparticles.

Agglomeration / nanopowder behaviour

The dustiness behaviour of nanoparticles is an important property. As mentioned in the previous bulletin, very few studies have explored this behaviour. For materials, where nanoparticles do not become readily airborne under normal handling procedures, the associated risk from inhalation will be considerably reduced.

Studies of robustness of industrial aciniform aggregates and agglomerates-carbon black and amorphous silicas: A review amplified by new data. Charles A Gray; Henry Muranko. [1]

A paper investigating the behaviour of carbon black and amorphous silica powders subject to uniaxial compression, mixing into rubbers and intense ultrasonication has been published. The authors concluded that severe mechanical processing of carbon black and amorphous silica caused moderate breakage of the largest aggregates and minimal liberation of primary particles. As shown by AD Maynard and al (2004) [2] during the handling of single-walled carbon nanotubes, this paper gives further evidence of the difficulties to breakdown aggregates and to liberate primary particles.

Laboratory simulation on nanoparticles containing materials

Evaluation of nanoparticle emmision for TiO_2 nanopowder coating materials. Li-Yeh Hsu and Hung-Min Chein. [3]

A paper on the evaluation of nanoparticles emission from TiO_2 nanopowder coating on substrates (tile, polymer film and wood) in a simulated box has been published. Sunlight, wind and human contact were simulated with UV light, a fan and a rubber knife. Measurements were carried out using a scanning mobility particle sizer (SMPS). The authors have shown that the highest emission was from TiO_2/tile (22 000/cm^3 at 55nm), with the emission rate still increasing after 2 hours. The particle number concentration decreased significantly after 60 and 90 minutes for TiO_2/polymer film and TiO_2/wood.

1.2 Measuring and monitoring of airborne nanoparticles

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 against characterised airborne nanoparticles or by laboratory inter-comparison studies. It is also necessary to develop methodologies for the calibration of instruments. Few papers have been published on the evaluation and calibration of these types of instruments .

Possible sampling artifact in real time particle size distributions related to sampling rate. Xiaohong Yao; Chak K. Chan; Ngai Ting Lau; P. S. Lau; Ming Fang. [4]

It is important that instruments measuring airborne nanoparticles or ultrafines are fast enough to capture the full spectrum of the particle size distribution especially in rapidly random changing concentration environments. This paper investigates the sampling rate issue of particle sizers for time periods in the range of 1s to 30s. The authors measured ultrafine particle size distributions in vehicle plumes in Hong Kong using an Electrical Low Pressure Impactor (ELPI gives particle size distribution in 12 size stages; 0.03 to 20 μm at scan rate of 1s). The data were used to construct the particle size distribution spectrum of a 30s scan rate Scanning Mobility Particle Sizer (SMPS). The authors found possible artefacts associated with slower scanning series for the measurement of particle size distributions in random rapidly changing high concentration environments such as road sides or tunnels. The outcome of this paper should be considered when measuring exposure to engineered nanoparticles in workplaces from processes susceptible to generate random and short time scale high concentrations.

Detection efficiency of a water-based TSI condensation particle counter 3785. T Petäjä; G. Mordas; H Manninen; P.P Aalto; K Hämeri; M Kulmala. [5]

This paper investigates the detection efficiency of a recently developed water based TSI condensation particle counter (CPC) (3785). CPCs provide real time number concentration measurements using water or solvents as a condensing fluid to enlarge nanoparticles so they can be detected by optical techniques. It is suggested that the cut-off diameter (minimum size of particles. detected with 50% efficiency) of the TSI 3785 were:

- 4 to 14nm for silver particles as a function of temperature difference between the saturator and the growth tube
- 5.1 and 3.6-3.8 nm for ammonium sulphate and sodium chloride respectively
- 5.8 nm for hydrophobic silver nanoparticles.

The authors found a detection limit for this instrument similar to the limit of solvent based CPCs (without the potential health and environmental problems associated with the use of solvents).

Instruments, such as diffusion charger (DC), Scanning Mobility Particle Sizer (SMPS) or Electrical Low Pressure Impactor (ELPI) used for measuring aerosols, modify the electrical charge on particles before detection. It is important to understand and measure the effectiveness of electrical aerosol chargers since the counting efficiency depends on their performance.

Two publications (Part I and Part II) investigating the effective electrical charging for instruments have been published [6, 7]. Part I reviews the performance criteria of electrical aerosol chargers in terms of charging effectiveness versus particle losses. A framework is presented for characterising and quantitatively comparing the performance of electrical aerosol chargers. In Part II, the framework is applied to the literature and to new measurements.

In addition to concentration levels of airborne nanoparticles, the physical and chemical characteristics of the engineered nanoparticles are important parameters for discrimination against natural ultrafine particles or those produced from combustion. An article discussing critical factors for off-line size distribution of airborne nanoparticles by Transmission Electron Microscopy (TEM) / Scanning Transmission Electron Microscopy (STEM) has been published [8]. These factors include magnification calibration, sampling, image analysis, beam exposure and particle shape. The authors found a good correlation of particle size distributions between TEM/STEM and Differential Mobility Analyser (DMA) measurements when analysing aerosol gold nanoparticles. In recent years, a number of articles have been published on the use of TEM for off-line physical and chemical analysis of airborne nanoparticles.

Standards and generation of airborne nanoparticles

Metal nanoparticle generation using a small ceramic heater with a local heating area. Jae Hee Jung, Hyun Cheol Oh, Hyung Soo Noh, Jun Ho Ji and Sang Soo Kim. [9]

The authors evaluated the performance of a small ceramic heater with a local heating area as an aerosol generator of silver nanoparticles. The particle size distribution of the aerosol was measured using a SMPS and the morphology, phase composition and crystallinity properties of the naoparticles were analysed by Transmission Electron microscopy (TEM) and X-Ray Diffraction (XRD). This simple and stable method is an alternative method to the tube-furnace evaporation / condensation generation system and could be used for the calibration and testing of instruments measuring airborne nanoparticles.

A paper on standard particles for the calibration of differential mobility analysers (DMAs) has been identified [10]. The authors suggested that poly(amidoamine) dendrimers are useful as standard particles in the range of a few nanometers.

Development of instruments

A number of articles reporting improvement and development of instruments and techniques for monitoring nanoaerosol exposure have been published. This includes:

- A new fast integrated mobility spectrometer for real-time measurement of aerosol size distribution [11, 12].
- A nano-DMA with no voltage change between aerosol inlet and outlet slits [13]. This instrument has been experimentally tested for ions with mobility diameter of 1.44 nm.
- A new type of differential mobility analyser (DMA) using longitudinal and transversal electrodes for the measurement of particle size distributions of aerosols over the full range of size [14]. This paper reports conceptual developments.
- A method for probing the physical structure of airborne nanoparticles aggregates by combining Differential Mobility Analysis (DMA) with Aerosol Particle Mass Analysis (APM) [15].
- An axial flow cyclone to remove nanoparticles at low pressure conditions [16].

New fast integrated mobility spectrometer for real-time measurement of aerosol size distribution: II. Design, calibration, and performance characterization. Pramod Kulkarni and Jian Wang. [12]

A fast Integrated Mobility Spectrometer (FIMS) for submicron particles has been developed. This instrument classifies charged particles based on their electrical mobility into different trajectories, the electrical field being constant. The particles are grown into droplets and their locations on the trajectories are measured by a fast charge-coupled device (CCD). In comparison with a Condensation Particle Counter (CPC), the authors found that the counting efficiency of the FIMS is 100% for particles greater than 20nm and higher than the CPC for particles with diameters less than 15nm. The authors claimed that compared to other instruments (such as Scanning Mobility Particle Sizer (SMPS)), the measurements speed and counting statistics are significantly improved.

Measuring particle size-dependent physicochemical structure in airborne single walled carbon nanotube agglomerates. Andrew D Maynard, Bon Ki Ku, Mark Emery, Mark Stolzenburg and Peter H McMurry. [15]

A method for probing the physical structure of airborne single walled carbon nanotubes (SWCNTs) aggregates by combining Differential Mobility Analysis (DMA) with Aerosol Particle Mass Analysis (APM) was developed. A structure parameter Γ (proportional to the square of particle mobility diameter divided by APM voltage) was calculated. The authors measured Γ for SWCNTs derived particles with mobility diameters of 31 nm and 150 nm. They showed that physical structure of aerosol particle released during handling of nanopowders may vary significantly depending on primary particle size and production batch.

An axial flow cyclone to remove nanoparticles at low pressure conditions. Sheng Chieh Chen and Chuen Jinn Tsai. [16]

This paper investigates the performance of an axial flow cyclone operating at low pressure ($5.7\ 10^{-3}$ to $9.3\ 10^{-3}$ Bars) for the removal of liquid oleic acid (OA) and sodium chloride nanoparticles in the diameter from 12 to 100nm has been published. Cyclones are normally used to collect particles in aerodynamic diameter greater than 5-10 µm. The cut off diameter can be reduced by reducing the cyclone diameter or increasing the flow rate. In this paper, the authors found that:

- The smallest cutoff aerodynamic diameters for OA and NaCl nanoparticles were 21 nm (cyclone inlet pressure: $5.7\ 10^{-3}$ Bars; flow rate: 0.35 l/min) and 21.2 nm ($7.2\ 10^{-3}$ Bars; 0.45 l/min) respectively.

This paper is of interest for the size selective sampling and exposure measurement of airborne nanoparticles.

Recent toxicological studies have shown the importance of measuring particle surface area for assessing exposure to nanoparticles in relation to potential health effects. For the same amount of mass, nanoparticles have an increasing total surface area with decreasing particle size. An instrument, which measure the lung deposited nanoparticle surface area in the alveolar and tracheobronchial regions is needed. Few instruments are available to measure directly particle surface area (eg. Diffusion chargers: LQ1-DC Matter Engineering and TSI 3070a Electrical Aerosol Detector (EAD)). Recent studies have shown that modification of the trap voltage in EAD allowed the measurement of the deposited nanoparticle surface area for different regions of the human respiratory system. TSI have developed a Nanoparticle Surface Area Monitor (NSAM) Model 3550, which measures total surface area deposited in tracheobronchiol and alveolar regions of human lung. A number of publications on lung deposited nanoparticle surface area measurement have been published:

- Rationale and principle of an instrument measuring lung deposited nanoparticle surface [17].

- **Calibration and numerical simulation of Nanoparticle Surface Area Monitor (TSI Model 3550 NSAM).** WG Shin, DYH Pui, H Fissan, S Neumann and A Trampe [18]. The authors experimentally determined the response function and calibration factors of NSAM using monodisperse aerosols (silver agglomerates and sodium chloride (7-100 nm)) and polydisperse aerosols (silver agglomerates number count mean diameter below 50 nm). The authors showed a linear relation between the currents and the total deposited nanoparticles surface area for the two regions of the lung. They claimed that monodisperse and polydisperse aerosols of nanoparticles can be used for the calibration of the NSAM for both alveolar and tracheobronchial regions as long as their sizes or size ranges are comparable with the required response function.
- Use of the electrical aerosol detector as an indicator of the surface area of fine particles deposited in the lung [19]. In this paper the authors calculated the particle surface area deposited in the lung using atmospheric particle size distributions measured in Mineapolis (USA) by a Electrical Aerosol Detector (EAD 3070).

Various instruments and methods, which can be used to measure mass concentrations or mass distributions of ultrafines or nanoparticles may not be accurate, may be affected by artefacts or may be time consuming. A paper reporting a new software algorithm to calculate diesel soot mass concentration in real time from spectral data produced by a particle size spectrometer (Cambustion DMS 500) has been published [20]. This paper is of interest to measure in real time mass concentrations of engineered nanoparticles in workplaces.

Biological monitoring of nanoparticles

Biological monitoring, by analysis of what comes out of the body, is a well established way of assessing the dose of chemicals that actually entered the body. Two papers on the biological monitoring of nanoparticles have been identified.

Stable isotopic tracing - a way forward to nanotechnology. Gulson B; Wong H. [21]

This paper discusses monitoring exposure to nanoparticles in the workplace using stable isotope tracers has been published. It is suggested that a stable isotope is incorporated in the material at the production stage. Workers' exposure could be monitored by taking dermal (using wipes), blood or urine samples and using analytical techniques such as inductively coupled mass spectrometry (ICPMS). Researchers in Australia are investigating its use to monitor the penetration of TiO_2 by dermal absorption. It is also suggested that workplace air measurement could be carried out.

A paper on the development of a method for trace analysis of fullerenes in biological samples has been published [22]. This method, based on liquid-liquid extraction and high performance liquid chromatography, was used for trace analysis of fullerenes in biological samples containing proteins and tape-stripped skin samples.

1.3 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 articles investigating nanoparticle penetration through filters have been published.

A comparison of two nano-sized particle air filtration tests in the diameter range of 10 to 400 nanometers. Daniel A Japuntich, Luke M Franklin, David Y Pui, Thomas H Kuehn, Seong Chan Kim and Andrew S Viner. [23]

The authors investigated two different filter test methodologies in the 10 to 400 nm particle size range (using aerosols of dioctyl phtlhalate (DOP) and sodium chloride):

- The commercially available TSI 8160 automated tester filter (comprising of an aerosol generator and a particle counter). In this system, the filter is challenged with very narrow particle size distribution aersosols produced using a differential mobility analyser (DMA) and electrically neutralized. The concentrations upstream and downstream of the filter are measured using Condensation Particle Counters (CPCs) and the penetration value is calculated.
- An assembled system, where a filter is challenged with a wide particle size distribution aerosol (electrically neutralized) and the concentrations upstream and downstream are measured using a Scanning Mobility Particle Sizer (SMPS).

Four medium efficiency fibreglass filter papers were used. Data were collected at volume flow rate of 32 l/min (face velocity of 5.3 cm/s). The paper discusses test variables. The authors found that:

- TSI 8160 can produce repeatable and reliable data for very narrow particle size penetration measurement with minor limitations.
- Percentage penetration values versus particle size obtained with the assembled system using a SMPS compared very well with TSI 81600 data.
- Following proper procedures, the filter penetration decreased as particle size decreased below 100 nm. This is in agreement with the theoretical Brownian capture model for uncharged particles down to 10 nm. The authors were reasonably confident that there is no evidence of particle thermal rebound.

Experimental study of nanoparticles penetration through commercial filter media. Seong Chan Kim, Matthew S Harrington and David Y H Pui. [24]

The authors investigated the nanoparticle filtration characteristics of a wide range of commercial filter media (four fibreglass filter media, four electret filter media, one nanofiber filter) using silver nanoparticles (from 3 to 20 nm) at face velocity of 5.3, 10, 15 cm/s. After size classification and neutralisation of the silver aerosol using a nanoDMA, the concentrations upstream and downstream of the filters were measured using Condensation Particle Counters (CPCs). The authors found that:

- Particle penetration decreased as particle size decreased (down to 3 nm).
- No significant evidence of nanoparticle thermal rebound.

A paper evaluating the pressure drop and penetration through polysulfone membrane filters for monodisperse polystyrene latex aerosols (sizes ranging from 38nm to 810 nm) using a Condensation particle Counter (CPC) has been published [25]. The measurements were carried out upstream and downstream of the filters at different flow rates and relative humidity. PLS filters may be used for aerosol sampling and air purification.

A paper on the application of nanofibers to improve the filtration efficiency of the most penetrating aerosol particles in fibrous filters have also been identified [26].

1.4 Control Measures

Two papers have been identified in this section:

- A paper looking at the effectiveness of control measures to reduce exposure to welding nanoparticles [27].
- An article reporting on improvement of electrostatic precipitator for the removal of sub-micron particles before their release to the environment has been identified [28]. The authors investigated the collection efficiency of a laboratory scale two-stage and barrier discharge type ESP using nano-sized particles of NaCl (30–100 nm) and Dioctyl sebacate DOS (50–800 nm).

Reduction of nanoparticle exposure to welding aerosols by modification of the ventilation system in a workplace. Myong Hwa Lee, William J McClellan, Joe Candela, Dan Andrews and Pratim Biswas. [27]

This paper reports on the performance of ventilation systems (booths) in reducing nanoparticle exposure to welding aerosols. The authors showed a reduction of particle number concentrations from 7.78 10^5 particles/cm^3 to 1.48 10^4 particles/cm^3 in the vicinity of welder's face during horizontal standard arc welding. The clearance of nanoparticles was also faster in the modified booth (6 minutes compared to 11 minutes). This article may be useful to establish methodologies of measurement and control of engineered nanoparticles in the workplace during handling.

1.5 Bibliography of key papers

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16 Sheng Chieh Chen and Chuen Jinn Tsai. An axial flow cyclone to remove nanoparticles at low pressure conditions. Journal of Nanoparticle Research, 9, 71-83, 2007.

17. H Fissan, S Neumann, A Trampe, DYH Pui and WG Shin. Rationale and principle of an instrument measuring lung deposited nanoparticle surface area. Journal of Nanoparticle Research, 9, 53-59, 2007.

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2. HEALTH EFFECTS

The majority of the publications (57%) retrieved by the health effects searches in the period December 2006 to March 2007 described effects of engineered nanoparticles in *in vitro* systems (Figure 2), with 37% describing effects in human cells grown *in vitro* and 20% in animal cells. Compared to the previous bulletin, there were relatively few reports of the effects of nanoparticles in animals (14%). No studies were noted in the areas of human or animal biomarkers or computational toxicology. 12% of the publications retrieved were reviews.

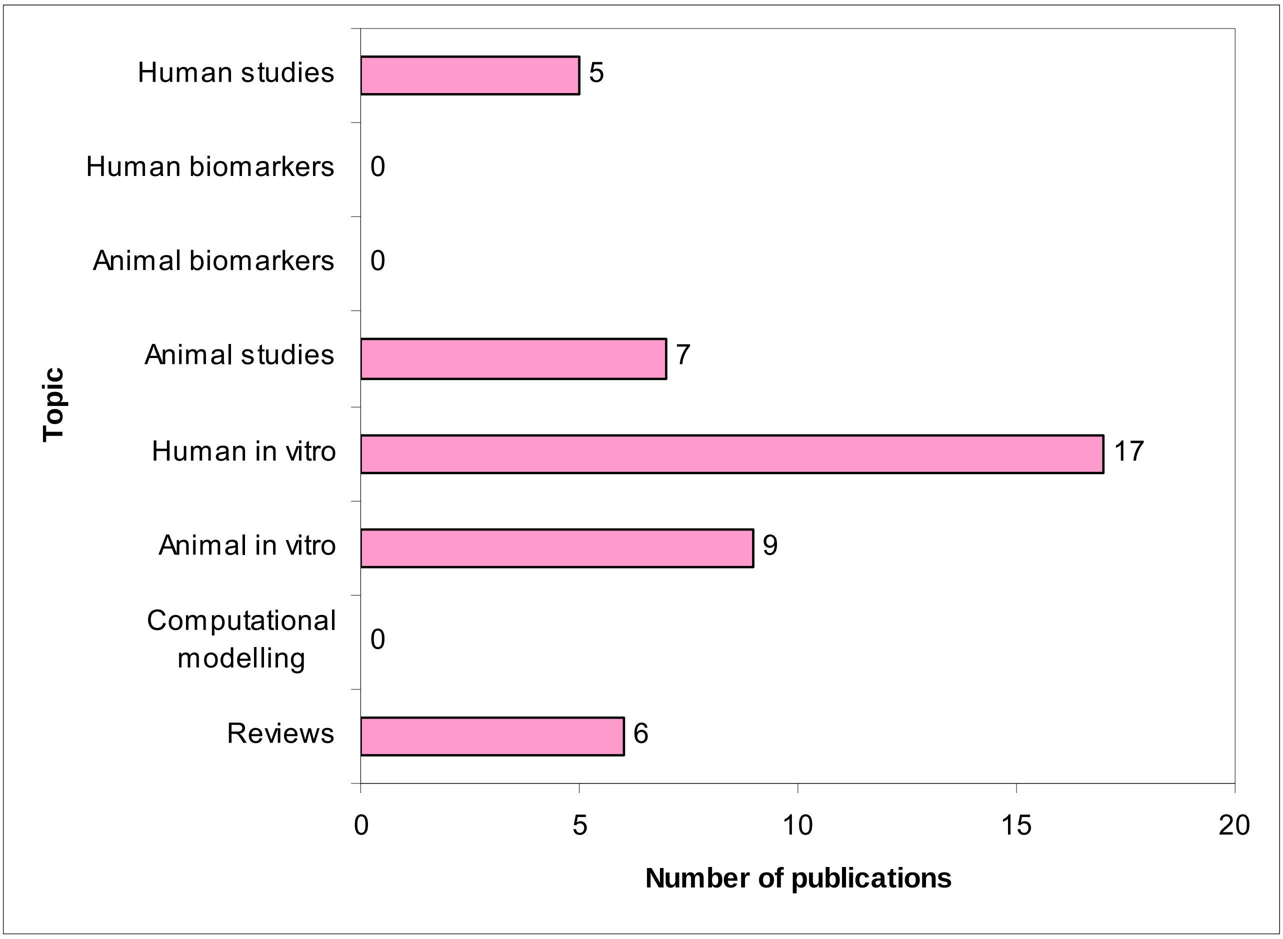

Figure 2: Breakdown per topic of the numbers of publications in the 4 months from December 2006 to March 2007 on the human health effects of *engineered* nanoparticles.

2.1 Human studies and epidemiology

One human study dating from March 2006 was identified in the present searches (via Laboratory Hazards Bulletin), which was not reported in the December issue of this bulletin. This study investigated the cancer risks in carbon black (CB) workers, building on the few previous cohort studies:

Cancer mortality in German carbon black workers 1976-1998. Wellmann et al (2006) [1]

In 1996 IARC reclassified carbon black as possibly carcinogenic to humans (Group 2B), based on sufficient evidence for carcinogenicity in animals but inadequate evidence in humans. The methodological problems or lack of information on the smoking habits of workers in the previous human studies prompted the authors to investigate the vital status and causes of death over the period 1976-1998 for 1535 male workers who had been employed at a German CB manufacturing plant for at least one year between 1960 and 1998. Smoking habits were taken into account. The standard mortality ratios (SMR)[1] for all cause mortality were increased for the CB workers, but they did not correlate with occupational histories and the likely exposures that workers received in different parts of the plant. **The data therefore do *not* suggest a link between length of CB exposure in the plant and death from lung (or any other) cancer.**

The data from this cohort of workers have been further analysed [2-4], and these reports agree with the conclusion that CB exposure is not linked to human lung cancer. Another cohort mortality study of CB workers has been carried out in US CB plants:

A cohort mortality study of employees in the U.S. carbon black industry. Dell et al (2006) [5]

Data on the mortality of 5011 workers employed for one year or more between 1930 and 2003 in 18 CB facilities in the US were assessed, and age-, race-, sex- and calendar year-adjusted SMRs were calculated. **The conclusions were that employment in the CB industry is not associated with increased mortality, increased cancer or specifically increased lung cancer**, although there is no indication in the abstract of whether the data were adjusted for the smoking habits of the workers.

Much of the data on CB tumorigenicity (epidemiology and laboratory animal studies) over the period 1996 to 2006 has recently been reviewed [6], leading to the conclusion that although some studies report associations between occupational exposure to CB and cancer risk, the larger studies do not report increased risk or a dose-response effect. Although rats develop lung tumours following administration of CB, these cancers are suggested to relate to particle overload more than particle chemistry, and may be of little relevance to humans.

2.2 Animal *in vivo* studies

Seven animal studies were retrieved in the health effects searches, all of which are summarised below. One study compared the effects of nano- versus micron-sized silicon dioxide on spermatogenesis in rats, and has implications for potential reprotoxicity of nanoparticles, although the particle metric used was mass-based concentration (mg/m^3) rather than particle number or surface area:

Comparative study of nanosized and microsized silicon dioxide on spermatogenesis function of male rats. Yi-Ou et al (2006) [7]

Rats were exposed to 100 or 300 mg/m^3 nano- or micron-sized silicon dioxide by inhalation for 2h every other day for 65 days, and the effects on testes and sperm were analysed, compared to control animals exposed to air. The sizes of the particles were not specified in the article abstract. The nano-SiO_2 induced more marked effects than the micron-sized particles, including reduction in sperm counts and histopathological changes.

A second study confirmed these results in rat sperm with magnetic nanoparticles [8].

All of the other studies examined the effects of nanoparticles on the rodent respiratory tract, the first suggesting that nanoscale titanium dioxide can induce emphysema-like disease in mice:

Titanium dioxide nanoparticles induce emphysema-like lung injury in mice. Huei-Wen et al (2006) [9]

This study builds on previous reports of the pro-inflammatory effects of inhaling nanoparticles and the increased effects of nano-sized versus micron-sized particles. Mice were exposed

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[1] The SMR compares the observed number of deaths with the expected number, based on national or regional reference rates.

by intratracheal administration to a single dose of 0.1 or 0.5 mg nano-titanium dioxide (19-21 nm) and assessed 3, 7 and 14 days later. The nanoparticles induced pulmonary emphysema, accumulation of macrophages, extensive alveolar damage, and type II cell hyperplasia, as well as up-regulation of many genes including chemokines, and many involved in cell cycle regulation and apoptosis. No control particles were mentioned.

The second study examined the role of particle size in allergic inflammation and sensitisation:

Ultrafine but not fine particulate matter causes airway inflammation and allergic airway sensitization to co-administered antigen in mice. De Haar et al (2006) [10]

Fine (250 or 260 nm) or ultrafine (29 or 14 nm) TiO_2 or CB were administered to mice intranasally, on an equal mass basis (200 μg), either alone or with ovalbumin. Only the ultrafine (not the fine) TiO_2 or CB induced airway inflammation, increasing both cell numbers in the peribronchial lymph nodes and Th2 cytokines (IL-4, IL-5, IL-10 and IL-13) after 8 days. Only the nanoscale TiO_2 increased the levels of ovalbumin-specific IgE and IgG1 in the serum of animals after 21 days, whilst both nanosized TiO_2 and CB induced allergic airway inflammation after 28 days in response to ovalbumin challenges. **The authors suggest that the nanoparticles induce both airway inflammation and possess adjuvant activity.**

Three further papers describe pulmonary effects of different nanoparticles [11-13], the first exploring the species differences observed when CB is administered to animals:

A comparative dose-related response of several key pro- and anti-inflammatory mediators in the lungs of rats, mice, and hamsters after subchronic inhalation of carbon black. Carter et al (2006) [11]

To compare the species sensitivity to CB, rats, mice and hamsters were exposed to 1, 7 or 50 mg/m^3 for 13 weeks, and after 1 day, 3 or 11 months, the bronchoalveolar lavage (BAL) fluid was analysed. Although all three species showed a dose and time response to the CB in terms of cell number and levels of reactive oxygen and nitrogen species and cytokines in BAL fluid, the pro-inflammatory responses of the rats were greatest, whilst the mice and hamsters' responses were anti-inflammatory. **These results help to explain the species differences seen in inflammation and tumour formation in response to CB.**

The two other publications emphasise that surface characteristics can greatly influence pulmonary effects in animals [12; 13]:

Pulmonary bioassay studies with nanoscale and fine quartz particles in rats: toxicity is not dependent upon particle size but on surface characteristics. Warheit et al (2006) [12]

The pulmonary effects (inflammation, cytotoxicity) of different types (synthetic versus mined) and sizes (12 / 50 nm versus larger 300 / 500 nm) of quartz were compared in rats, 24h, 1 week, and 1 and 3 months following instillation. The particles had differential effects that correlated better with surface reactivity than particle size or surface area, with the sequence of effects descending in the order: 12 nm synthetic quartz II = mined 500 nm Min-U-Sil quartz > synthetic 300 nm quartz > 50 nm quartz I > carbonyl iron control particles (0.8-3 μm).

Pulmonary toxicity study in rats with three forms of ultrafine TiO_2 particles: differential responses related to surface properties. Warheit et al 2006 [13]

This study was similar to [12], but compared different forms of TiO_2. Whilst quartz (0.2-2μm) and to a lesser extent 80/20 anatase/rutile (~129 nm) TiO_2 induced pulmonary inflammation, cytotoxicity and adverse lung effects, the fine (~380 nm) rutile and two rutile TiO_2 nanoparticles (~136 and 149 nm) produced only transient inflammation. **These results again suggest that particle size is not the only predictor of toxicity, but crystal structure and surface reactivity are equally or more important parameters.**

One further animal study has investigated the toxicity of different sized TiO_2 particles in mice after oral gavage, a potentially less important route of delivery than inhalation, and reported no acute toxicity after 2 weeks [14]. Nanoparticles (25 and 80 nm) distributed to liver, spleen, kidneys and lung, and significant hepatic injury was observed.

2.3 *In vitro* studies

Of the 27 publications identified in this area by the health effects searches, 17 reported the effects of nanoparticles in different types of human cells *in vitro*, and will be considered first, since they are considered to be of higher priority than studies in animal cells. Two of the retrieved publications considered the potential genotoxicity of TiO_2 nanoparticles and C60 fullerenes suspended in water [15; 16]. Both of these publications are summarised below, since they used methods for assessing genotoxicity that are accepted for regulatory purposes.

Cyto- and genotoxicity of ultrafine TiO2 particles in cultured human lymphoblastoid cells. Wang et al (2007) [15]

The cytotoxicity and genotoxicity of nanoparticles of TiO_2 (<100 nm) were investigated in WIL2-NS cells. There were dose and time dependent (0-130 μg/ml; 6, 24 and 48h) losses of cell viability by MTT assay, which were significant at the higher doses and longer incubations. 130 μg/ml TiO_2 increased the frequency of micronucleated binucleated cells and reduced the cytokinesis block proliferation index in the cytokinesis block micronucleus assay (CBMN), and increased the mutation frequency in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) gene mutation assay. 65 μg/ml TiO_2 increased the olive tail moment in the Comet assay, a measure of DNA damage. **The authors conclude that nano-sized TiO_2 can cause significant cyto- and genotoxicity in human cells.**

Stable colloidal dispersions of C60 fullerenes in water: evidence for genotoxicity. Dhawan et al (2006) [16]

Extended mixing of C60 fullerenes in water results in larger colloids than those prepared by ethanol to water exchange. The genotoxicity of the two suspensions was compared in human lymphocytes using the Comet assay; the genotoxic response correlated with the C60 concentration for both colloids, but the response was greater for the aqueous suspension for a given C60 concentration.

Three papers report the effects of **carbon nanotubes** (CNTs) in human cells *in vitro* [17-19]. These studies largely confirm other reports on CNTs, although two of the reports suggest low toxicity of the CNTs. A comparison of the effects of different types of carbon nanomaterials in human fibroblasts revealed that the best predictor of toxicity is particle surface area, and refined single-walled CNTs (SWCNTs) are more toxic than unrefined SWCNTs, CB, carbon graphite or multi-walled (MW) CNTs [19]. In contrast, in A549 human lung cells, SWCNTs displayed low acute toxicity and were not detected intracellularly, but the CNTs interfered with several of the dyes used in the assays [17]. Similarly, in human A549 cells and rat macrophages (NR8383), none of the carbon nanomaterials evaluated (SWCNTs, MWCNTs, CB or quartz) were toxic or induced generation of the inflammatory mediators NO, TNFα or IL-8, although in this report, the CNTs did cross the cell membrane [18]. However all the CNTs (except for a SWCNT preparation that had been purified with acid) led to a dose- and time-dependent increase in reactive oxygen species in the cells and a loss of mitochondrial membrane potential. The authors concluded that the traces of metal catalyst in the CNTs caused the biological effects [18], and it is possible that differences in purity of carbon nanomaterials could partly explain the differences reported by different authors.

A549 cells have also been used to investigate the toxicity *in vitro* of nanoparticles of cerium oxide [20], silica [21], TiO_2 [22], and vanadium oxide [23]. Dose- and time-dependent increases in oxidative stress and loss of viability were reported for 20 nm cerium oxide particles [20], and 15 nm / 46 nm silica nanoparticles [21]. Needle-like nanoparticles of vanadium oxide (V_2O_3), less than 30 nm in diameter and of variable lengths, were considerably more toxic (10 fold) than bulk-sized material in endothelial and epithelial cells (ECV304 and A549 cells respectively) [23]. The V_2O_3 nanofibres also led to changes in the levels of heme-oxygenase 1, and lipid peroxidation in mouse macrophages (RAW cells), all effects implicated in cellular oxidative stress. Nanoparticles of TiO_2 induced dose- and time-dependent cytotoxicity and inflammation in A549 and HDF cells *in vitro* [22]. As observed in *in vivo* studies [13], the cytotoxicity and generation of reactive oxygen species (ROS) correlated best with the phase composition of the particles rather than surface area, such that anatase TiO_2 was 100 fold more toxic than the rutile form. The authors conclude that TiO_2 particles that are optimised for photocatalytic effects are also more likely to generate ROS in cells.

In contrast, metal oxide nanoparticles (Al_2O_3, CeO_2, Fe_2O_3, NiO, SiO_2 or TiO_2) induced less of the pro-inflammatory cytokines, IL-6 and IL-8, than either micron-sized particles or soil-derived nanoparticles in BEAS-2B lung cells [24]; the authors noted problems however with detecting cytokines since they readily adsorb to the nanoparticles. Micron-sized cobalt particles inhibited release of the Th1/Th2 cytokines (IL-2, -4, -6, 10 and TNFα, IFNγ) in human peripheral blood mononuclear cells, whilst cobalt nanoparticles increased levels of TNFα and IFNγ [25], but potential interference with the assays was not mentioned.

Entry of micron-sized ($\leq$ 0.2 μm) and nanoparticles into human red blood cells has been detected using a range of different microscopic techniques, and found not to be influenced by the surface charge nor material of the particles [26]. The mechanism appears different to both phagocytosis and endocytosis.

The biocompatibility of quantum dots (QD) has been investigated in human neuroblastoma cells (SH-SY5Y), the authors noting that surface modifications with N-acetylcysteine reduce both QD internalisation and cytotoxicity [27]. Cytotoxicity correlated with Fas up-regulation, a signalling process associated with cell death.

Two publications report methodological advances for *in vitro* delivery of nanoparticles to human cells. One report describes a novel method in which C60 fullerenes in methanol are applied to culture dishes, and the solvent allowed to evaporate [28]. When plated on the dishes, several human mammary epithelial and hepatic cell lines took up the particles, but the C60 were neither cytotoxic nor anti-proliferative. The authors suggest that the method of dispersion and delivery of fullerenes to cells may greatly influence their subsequent effects. In the second paper, perfusion chambers were used to achieve homogeneous delivery of carbon nanoparticles on to the air-liquid interface of A549 cells, effectively mimicking *in vivo* exposure [29]. Cell viability was unaffected by growth in the chamber, and administration of the particles led to increased transcription of heme-oxygenase 1, but no cytotoxicity.

Studies in animal *in vitro* systems are considered to be of low priority for this bulletin, and therefore the nine reports identified by the health effects searches will be briefly summarised. However one report is given higher priority since it considers an alternative explanation for nanoparticle-induced decreases in alveolar clearance of test particles by macrophages *in vivo*: the authors propose that the decrease is directly proportional to the potential for the nanoparticles to mask the macrophage's surface [30].

Six studies examined the effects of different carbon nanoparticles, and noted that (i) iron-rich SWCNTs generate more ROS in stimulated mouse macrophages (RAW 264.7) than purified CNTs [31]; (ii) γ-irradiation of C60 fullerenes eliminates their cytotoxicity and leads to cytoprotective effects in a range of cells (e.g. human and rat glioma cells, primary rat macrophages) [32]; (iii) C60 fullerenes can form stable, water-soluble complexes with bovine serum albumin [33]; (iv) nanodiamonds (2-10 nm) are not cytotoxic and do not induce ROS in neuroblastoma cells, keratinocytes, macrophages or PC12 cells [34]; (v) different sizes of CB nanoparticles have differential oxidative effects in rat alveolar type II epithelial cells (SV40T2) and alveolar macrophages [35]; (vi) apoptosis and proliferation induced by carbon nanoparticles in rat lung epithelial cells are mediated by specific signalling pathways (ERK versus JNK respectively) [36]. In Neuro-2A mouse neuroblastoma cells, metal oxide nanoparticles (30-45 nm) have differential, dose-dependent effects: of TiO_2, ZnO, Fe_3O_4, Al_2O_3 and CrO_3, ZnO most potently induces morphological changes, decreases in mitochondrial function and LDH release [37]. In another nervous system model, BV2 microglia engulfed TiO_2 aggregates (826-2368 nm) formed from P25 nanoparticles, and although they were not cytotoxic, the particles induced a rapid and sustained release of ROS [38].

2.4 Reviews

Six reviews were identified from the health effects searches for the period December 2006 to March 2007. One review highlights an issue of concern for all *in vitro* studies, pointing out that nanoparticle particokinetics in culture systems can significantly alter the dose that cells actually receive, and hence the biological effects [39]. The authors propose an approach for simulation of these particokinetics *in vitro*.

The other five reviews focus largely on the potential risks of occupational and incidental exposure to nanomaterials [40-44], emphasising that strategic research and investment is required internationally to ensure that emerging nanoparticles and their applications are as safe as possible.

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3. CONTACTS

For more information please contact:

Measurement, exposure and control:

Delphine Bard (Analytical Sciences Section): (delphine.bard@hsl.gov.uk)	Tel: 01298 218558
Dave Mark (Exposure Control & Measurement Section): (dave.mark@hsl.gov.uk)	Tel: 01298 218550
Derrick Wake (Exposure Control & Measurement Section): (derrick.wake@hsl.gov.uk)	Tel: 01298 218529
Nick Vaughan (Personal Protection Equipment Section): (nick.vaughan@hsl.gov.uk)	Tel: 01298 218329

Health effects:

Rosemary Gibson (Health Exposures Section): rosemary.gibson@hsl.gov.uk	Tel: 01298 218675
Anna Rowbotham (Health Exposures Section) (anna.rowbotham@hsl.gov.uk)	Tel: 01298 218440
Gareth Evans (Health Exposures Section) (gareth.hsl.evans@hsl.gov.uk)	Tel: 01298 218410