Health & Safety Executive NanoAlert Service

**Prepared by the
Health & Safety Laboratory, Buxton, UK**

Bulletin Contents:

1. Measurement, exposure and control
2. Health effects
3. Contact details for HSL NanoAlert service team

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 have been published on the development, improvement and assessment of instruments for the measurement of airborne nanoparticles as well as on the characterisation of nanoparticles in their bulk form, in fluids or in biological tissues. Several papers were identified on the generation of standards nanoparticles for toxicity and instruments testing, an important topic in the field of health and safety. Once can see the emergence of studies reporting on the assessment of exposure to engineered nanoparticles in the workplace, including five papers on carbon nanotubes / fullerene and three papers on metal oxides. In terms of engineering control measures, a paper assessing the effectiveness of a local the effectiveness of a local exhaust ventilation (LEV) unit used during a reactor clean-up operation at a facility where nanomaterials were produced was identified. In this search, three papers of interest for this bulletin reviewing the measures to control exposure levels in the workplace and discussing the solutions to handle nanomaterials have also been identified: Papers proposing or discussing control banding or occupational risk management tools for the control of nanoparticles exposures are now emerging. Also, several papers have been published reporting on the efficiency of filters and for the first time, the search has retrieved a paper on the performance of disposable respirators worn by a human subject during exercises.
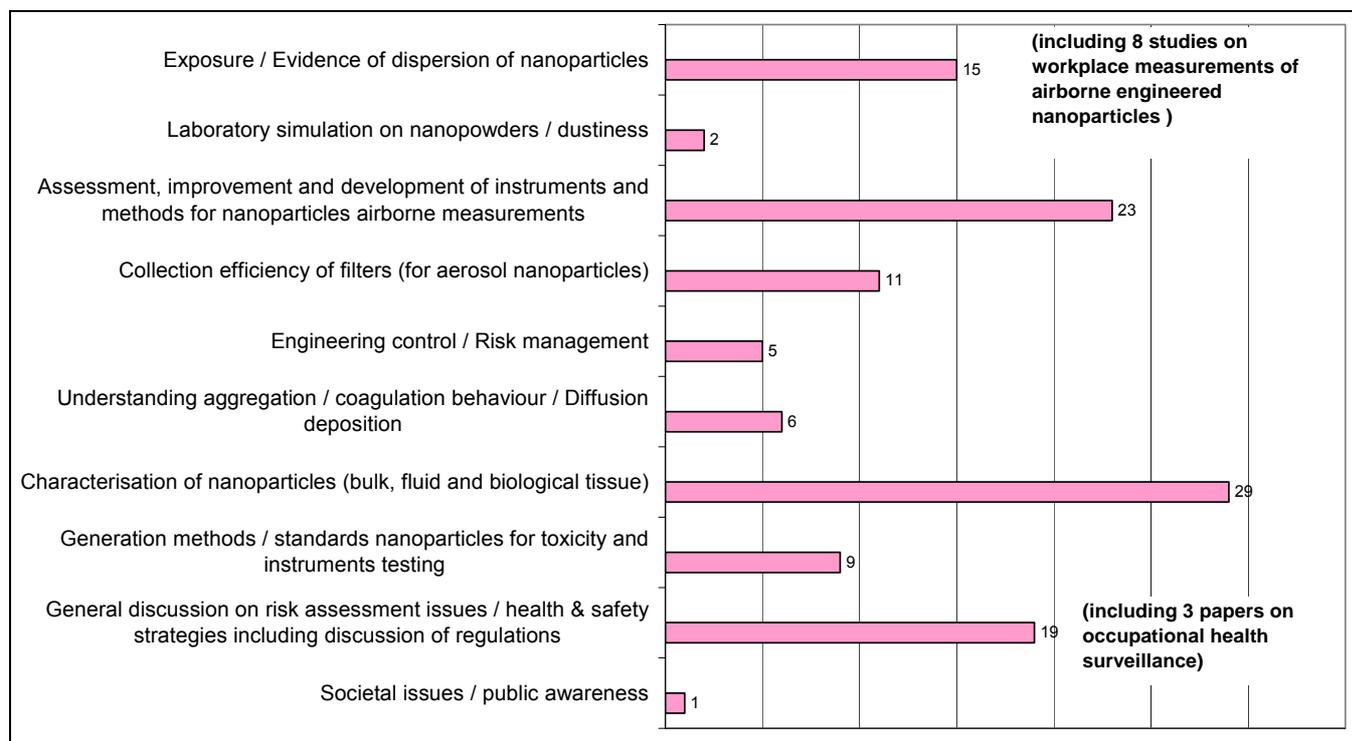

Figure 1: Breakdown of the number of papers per topic (measurement, exposure and control) retrieved in the ten months from March 2008 to December 2008.

1.1 Exposure data

1.1.1 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. There are many challenges to exposure measurements in the workplace including the discrimination of engineered nanoparticles against a background of "ultrafines" originating from different sources including urban pollution. Fujitani (2008) reviewed the methods for the measurement of nanoparticles in terms of size distribution, number, surface area and mass [1]. They also discussed the sources of airborne nanoparticles: environmental sources such as urban pollution and occupational setting sources generated from workplace activities such as bagging or cleaning activities using vacuum cleaners.

In this bulletin, a number of studies on the assessment of exposure level to engineered nanoparticles in the workplace have been published in peer-reviewed journals. One can observe the emergence of papers on workplace exposure measurements including those on carbon nanotubes.

Carbon nanotubes and fullerenes

Five main papers on exposure measurements to carbon nanotubes or fullerenes have identified from this search and are highlighted below.

Monitoring multiwalled carbon nanotube exposure in carbon nanotube research facility. Han et al (2008) [2].

The authors report on the monitoring of multiwalled carbon nanotubes (MWCNTs) in a MWCNTs research facility during the handling of unrefined MWCNTs. Personal and area air samples were collected onto 0.8 µm pore size mixed cellulose filters using a sampling pump running at 1.5-2 l/min. The filters were analysed using a scanning transmission electron microscopy (STEM) with an energy dispersive x-ray analyser. Real time measurements of number concentration and particle size distribution were performed using a scanning mobility particle sizer (SMPS) and an Aerodynamic Particle Sizer (APS). The mass concentration of black carbon was measured using an aethalometer. The authors found that:

- In the blending laboratory (laboratory formulating composites), the gravimetric concentrations of total dust ranged from 0.21 to 0.43 mg/m^3 before control during blending using an open blender to a negligible level after control. The number concentration of MWCNTs ranged from 172.9 to 193.6 MWCNTs/cm^3 before control (during blending operation using an open blender) and 0.018-0.05 MWCNTs/cm^3 after control. The diameter and length of the tubes were 52-56 nm and 1473-1760 nm respectively. The APS showed a relatively high concentration in the 2-3 µm range size.
- MWCNTs from STEM analysis were not detected in laboratory A (CNT manufacturing from furnace) and B (processing room for spraying) before control.

Exposure to nanoscale particles and fibers during machining of hybrid advanced composites containing carbon nanotubes. Bello et al (2008) [3].

The authors investigated airborne exposures to nanoparticles and fibres generated during dry and wet abrasive machining of two three-phase advanced composite systems containing carbon nanotubes (CNTs), micron-diameter continuous fibres (carbon or alumina), and thermoset polymer matrices. The authors found that wet cutting did not produce exposures

significantly different than background but dry cutting, without any emissions controls, provided a worst-case exposure. In general, airborne exposure levels were not significantly different for composites with and without CNTs. No CNTs were observed on collected samples after extensive electron microscopy. The mean number concentration for dry cutting was composite dependent and varied over an order of magnitude. The highest values were observed for thicker laminates at the source (>1×10^6 particles/cm^3). Concentration of respirable fibres for dry cutting at the source ranged from 2 to 4 fibers/cm^3 depending on the composite type.

Particle exposure levels during CVD growth and subsequent handling of vertically-aligned carbon nanotubes films. Bello et al (2008) [4].

The authors investigated the potential exposure to nanoparticles in a research laboratory during:
- the CVD growth of vertically-aligned forests of carbon nanotubes (CNTs) on a substrate in a tube furnace;
- the removal of the CNTs from the substrate using a razor blade, without local exhaust ventilation (LEV).

The whole process (furnace heating, CNT growth, furnace cool-down, opening of furnace removal of the substrate and mechanical removal of CNTs from the substrate) was monitored on three occasions using real-time instruments. The real-time instruments included a fast mobility particle sizer (FMPS) for size and number concentration measurements and a condensation particle counter (CPC) for number concentration measurements. Samples were also collected for electron microscopy analysis.

The authors found no detectable quantity of CNTs or bundles of CNTs during the growth or handling of CNTs.

Measurement of the physical properties of aerosols in a fullerene factory for inhalation exposure assessment. Fujitani et al (2008) [5].

The authors report on measurements carried out in a fullerene factory in Japan. Particle number concentrations and number size distributions were monitored using a scanning mobility particle sizer and an optical particle counter. Airborne samples were also collected on 47mm quartz fibre filters for scanning electron microscopy. Particle size distributions and morphology measurements were conducted during non-work periods and work-periods, during handling and an agitation process and at a nearby outdoor air in order to identify the sources of the particles. The authors found:
- During the removal of fullerenes from a storage tank for bagging and or weighing, the particle volume concentration* for particles > 1000nm was greater during the work period than during the non-work period. SEM confirmed the presence of aggregates/agglomerates of fullerenes.
- During the use of a vacuum cleaner, the particle number concentration for particles <50nm was greater during work period than during non-work period.
- During the agitation process, the calculated particle volume concentration* for particles in the coarse size range was also greater during the work period (80 to 150 times) than during the non-work period. SEM confirmed the presence of aggregates/agglomerates of fullerenes.

* Assuming particles are spherical.

Characterisation of airborne particles during production of carbonaceous nanomaterials. Yeganeh et al (2008) [6].

The authors reported a study conducted in 2005 and 2006 at a commercial facility in the United States producing fullerenes and other carbonaceous nanomaterials. Each production

run included two or three activities: arc reaction; sweeping out raw soot using a scoop and a brush; optional vacuuming of residual soot. The production reactor was in a fume hood. The measurements took place inside the fume hood, just outside the fume hood face (work zone), outside the fume hood about 2m away from the reactor (background).

There was no significant difference in the average PM2.5 mass concentration (measured using a light-scattering aerosol photometer) and the particle number concentration (measured using a scanning mobility particle sizer) between inside the facility and outside the facility. However, significant short-term increases in PM2.5 and particle number concentration were observed during the physical handling of nanomaterials (e.g. sweeping) or during other production activities. In many cases, the increase in the total number concentrations was mainly due to the increase in the sub-100nm number concentration. The airborne particles inside the fume hood, aerosolised during physical handling, were mainly carbonaceous particles whereas the airborne particles outside the fume hood (from other production activities such as drilling and cutting of graphite and metal) were not. Yeganeh (2008) concluded that the engineering control at the fullerene commercial facility appeared to be effective at limiting exposure to nanomaterials [6]. The measurements in this study did not differentiate between engineered nanomaterials and those carbonaceous particles from other sources.

Metal based / metal oxide nanoparticles

Three main papers on exposure measurements of metal based / metal oxide nanoparticles have identified from this search and are highlighted below.

Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods. Tsai et al (2008) [7].

The authors have monitored the airborne particle concentration during the handling of alumina (primary particle size from 27 to 56nm) and silver (average particle size of 60nm) nanoparticles in three fume hoods. The handling tasks included pouring and transferring using a spatula 100 and/or 15g of powder from one beaker to another. The hoods were conventional (>20 years of use), bypass (<5 years) and constant velocity (<1 year) type of hoods. It was tested with the sash at position high, middle and low. The minimum face velocity ranged from 0.3 to 0.5m/s. The particle number concentration and size distribution were measured using a fast mobility particle sizer (FMPS). Air samples were also collected for characterisation by electron microscopy. It was found that:

• The handling of dry powders inside fume hoods can result in a significant realese of airborne nanoparticles in the worker's breathing zone. The increase in particle number concentration during the handling of 100g of nanoalumina powder using a conventional hood was as high as 13 000 particles/cm^3 (low open sash, velocity of 1 m/s).

The authors' recommendations are:

• The face velocity of the fume hoods should be between 0.4 and 0.6m/s, with sash height being as low as possible.
• Constant velocity hoods should be preferred to compensating hoods, which in turn should be preferred to standard fume hoods.
• Air currents in the vicinity of the hood should be reduced / eliminated.
• The smallest amount of nanoparticles should be handled using the least energetic handling method.

Engineering case reports. Effectiveness of local exhaust ventilation (LEV) in controlling engineered nanomaterials emissions during reactor cleanout operations. Methner (2008) [8]

MM Methner from NIOSH assessed the effectiveness of a local exhaust ventilation (LEV) unit used during a reactor clean-up operation at a facility where materials (metal oxides nanoparticles e.g. manganese, silver cobalt) were produced via a gas phase condensation at a rate of one kg per day. Prior to this assessment, an initial investigation of work practices and controls was conducted and established uncontrolled source of engineered nanomaterials during the reactor cleanout procedure (brushing and scraping activities). Consequently NIOSH recommended the use of a LEV system during cleaning.

Particle number concentrations were monitored using a condensation particle counter and an instrument based on optical counting principles using laser light scattering. Airborne samples were also collected on filters for electron microscopy and gravimetric analysis. Background particle number concentration were measured before and after and subtracted to the process specific measurements.

The authors found dramatic reduction in emissions with the use of a LEV and the implementation of a more targeted brushing / scraping toward the inlet of the LEV. During reactor cleanout, the mass concentration ranged from 6700 to 710 µg/m^3 without LEV compared to 1700 to 41 µg/m^3 respectively with LEV. The adjusted number concentration ranged from 16917 to 6050 particles/cm^3 without LEV compared to 998 to 0 particles/cm^3 with LEV.

Exposure to manufactured nanostructured particles in an industrial pilot plant. Demou et al (2008) [9].

The authors monitored over a 25 day period the exposure level in a "nanostructured particle pilot scale production facility using gas phase process". The facility produced metal based nanoparticles embedded in a large porous oxide matrix. Temporal and spatial variations in particle concentrations and sizes were performed during production, handling and maintenance. The number concentration was measured using CPCs, the size distribution using a SMPS and the mass concentration using a Dust Trak ^{TM} monitor.

The background levels were measured but no physico- chemical analysis were performed. The authors found:

- Elevated number concentration during production, which can be an order of magnitude greater than the background (average concentration of 59 100 particles/cm^3 and 0.188 mg/m^3 for submicron particles). A concentration peak at ~ 200nm was observed during production and ~ 1/3 of the measured particles had a mobility diameter of <100nm.
- The vacuum cleaner (equipped with German "Dust Class M" filter was also a source for short term exposure (the chemical nature of particles were unknown).
- Particle handling and processing did not result in a substantial increase in submicron particle concentrations.

The authors also assessed the filter efficiency breathing mask filters under real-time production conditions. The authors found that:

- Under real-time production conditions, the filter efficiency of FFP3 and FFP2 (3M 2135FFP3; 3M 5935 FFP3; 3M 9320 FFP2; Dräger type 680FFP3) filters ranged between 96.66 and 99.99% in terms of number concentrations at flow rate between 1 and 3 m^3/h. It ranged between 99.999% and 99.989% for the FFP3 filters.

Other papers

Other papers of interest have been included in this bulletin and are briefly described below:

- A paper on the environmental exposure to cerium oxide nanoparticles from vehicles using Envirox has been retrieved from this search [10]. Park evaluated the safety in use of Envirox (cerium oxide nanoparticle based fuel-borne catalyst) at low levels of 5mg/l to reduce fuel consumption and the emission of combustion derived nanoparticles and un-burnt hydrocarbons [10]. In the study, the authors have assessed exposure from

modelling calculation and airborne monitoring at three sites in the UK (near roadsides along which vehicles using Envirox added diesel fuel operate).
The authors found from the airborne monitoring that:

- The emissions of cerium increased (fourfold) at one site (Newcastle) following the introduction of Envirox. This was due to the high proportion of buses using Envirox compared to the two other sites in London.
- The airborne concentration of cerium at the Newcastle site following the introduction of Envirox was of the same order than those at the London sites before the introduction of Envirox.

- A paper reporting a survey from Swiss companies gathering information on the manufacture and handling of nanomaterials in workplaces has been identified [11]. Schmid carried out a targeted telephone survey between July 2005 and February 2006 amongst health and safety representatives from 197 Swiss companies [11]. Forty-three companies used or produced nanoparticles. Eleven imported and traded pre-packaged goods containing nanoparticles.
  - Nanoparticles used in large quantities (several tons per year) were: iron oxides, TiO2, silver, aluminium oxide, zinc oxide and carbon black.
  - The size of reporting companies using nanoparticles was mainly middle size companies (50-249 employees).
  - The quantities of nanoparticles used or produced ranged from few grams to 1000 tons / year (mean quantity reported: 40t; median = 100kg/year).
  - Nanoparticles are used in many sectors including in more traditional sectors (e.g. paints).
  - In general, the safety measures were higher for companies working with nanopowders compared to those working with nanoliquids (7 of 22 companies with liquid only applications only used RPE as protective measures).

- Two papers on TiO_2 nanoparticles have also been included in this bulletin:
  - Liao (2009) "investigated the effects of particle size and phase composition of TiO_2 nanoparticles on human exposure to airborne nanoparticles during manufacturing activities" [12]. In this study the authors re-analysed published data of airborne nanoparticle concentrations and size distributions obtained in TiO_2 plants.
  - Liao (2008) developed a model-based approach to assess inhalation exposure risk levels to airborne fine/nano TiO_2 during manufacturing activities [13].

- A paper on the monitoring of ultrafine particle concentrations and size distribution in a iron foundry has been identified [14]. The authors measured the number and surface area concentration of nanoparticles produced by metal melting, pouring and molding processes.

1.1.2   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) [15]. 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. Recent studies have focussed on the development of modified dustiness testing method for nanopowders. These studies have explored the measurement of number concentration and size distribution of the aerosol generated from the dustiness testing

device, the down-sizing of the testing device or the use of more energetic system of disturbance.

In this issue, two papers on the dustiness behaviour of nanoparticles has been identified:

Dustiness behaviour of loose and compacted Bentonite and organoclay: What is the difference in exposure risk? Jensen et al (2008) [16].

The authors have investigated the dustiness of loose and compacted montmorillonite Bentonite and an organoclay (Nanofil®5) using a combined single drop and rotating drum test (see NanoAlert Issue 5). The size distributions and number concentrations were measured in the drum using a fast mobility particle sizer and an aerodynamic particle sizer. The dustiness indexes in mg / kg of test material were calculated from the mass of dust collected on a filter. The authors found that:

- Nanofil 5, compacted Bentonite and Bentonite showed intermediate dustiness indicies (1077-2077 mg/kg). A high level dustiness index was found for compacted Nanofil 5 (3487 mg/kg).

- The samples produced bi or tri-modal particle size-distributions of aggregated and / or agglomerated particles. The particle size modes occurred between 300 and 400nm as well as between 1.2 and 3 μm.

- The dust release occurred as a burst for loose Bentonite and Nanofil5, as a constant rate for compacted Nanofil5 or as a slowly increasing rate for compacted Bentonite.

- For bentonite, compaction (at $3.5kg/cm^2$) reduced the dustiness index by about 20%. It reduced the number concentration by ~40% in the rotating drum and by ~70% in the single drop test.

- For Nanofil 5, compaction increased the dustiness index by ~ 220%. In the rotating drum, the compaction increased the particle number concentration by 242 / 147% (FMPS/APS)*. In the single drop test, the number concentration measured with the FMPS was almost the same for compact and non-compact Nanofil5. The number concentration measured with the APS was 50% lower for compact compared to non-compact Nanofil5 in the single drop test.

FMPS: Fast Mobility Particle Sizer

APS: Aerodynamic Particle Sizer

Dustiness test of nanopowders using a standard rotating drum with a modified sampling train. Tsai et al. (2009) [17].

In this study, the authors carried out measurements using the standard rotating drum method described in EN 15051 (2006) and a modified version. In the modified version, a scanning mobility particle sizer (SMPS), APS (Aerodynamic Particle Sizer) and a MSP MOUDI (micro-orifice uniform deposit impactor) was connected to the sampling train of the drum (the filter was removed but the 20 and 80 ppi porous foams were left in the sampling device). TiO_2 nanopowder (Degussa Aeroxite TiO_2 P25) and fine ZnO (Sun Beam, Grade A, Taiwan) were tested in the standard (for 1 minute) and modified drum (for 30 minutes), at a rotation speed of 4 revolutions per minutes. The authors found that:
- The average inhalable, thoracic and respirable fraction for TiO_2 (crystallite size of 21nm and bulk density of $0.13g/cm^3$) was 6713 ± 546 (high); 576 ± 37 (moderate); and 15 ± 2 (low) mg/kg respectively.

- The average inhalable, thoracic and respirable fraction for ZnO (crystallite size of 250-300nm and bulk density of 0.6g/cm^3) was 142 (very low) $\pm$ 20; 72 $\pm$ 6 (low); and 11 $\pm$ 0.3 (low) mg/kg respectively.
- Real time instruments showed that very few particles less than 100nm were generated and the number concentration of submicron particles was higher for TiO$_2$ than ZnO.

Also of interest is the paper from Schwager (2008). The authors investigated the fractal structural evolution of a nanopowder by repeated dispersion and settling using a numerical model [18].

1.2   Measuring and monitoring of airborne nanoparticles

It is critical to determine ambient or background particle concentrations before measuring particle concentrations during the manufacture or handling of the nanomaterials. However, the background nanoparticle concentrations can vary spatially and temporally making exposure quantification challenging. In this paper, Seipenbusch (2008) investigated the temporal evolution of engineered nanoparticle aerosols in a workplace simulated environment using a test chamber [19]. The authors assessed the engineered nanoparticle release into a particle free background environment and the release in the presence of a pre-existing background aerosol. The authors found that the aerosols changed in size and number concentration by coagulation, homogeneously by coagulation within the nanoparticle size class or heterogeneously by interaction with the background aerosol. These changes depended on the concentration and particle size of the background aerosol and the number concentration of the engineered nanoparticle aerosol. The authors also observed that binary particles consisting of background particles and engineered nanoparticles evolve, constituting a change in chemical composition.

It has been reported that nanoparticles numbers does matter when estimating risk and that both nanoparticle number and surface area are relevant. 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 on the evaluation and development / improvement of instruments or methodology (better resolution, multifunctional, faster response, improved charging performance) for exposure measurements of nanoparticles have been published. A few papers reporting on the design and development of compact monitors, which are much sought after by occupational hygienists, have also been identified.

1.2.1   New / extended methodology / instruments

A number of papers reporting new / extended methodology / instruments for the measurement of airborne nanoparticles have been identified in this search.

Conceptual limitations and extensions of lung-deposited Nanoparticle Surface Area Monitor (NSAM). Asbach et al (2009) [20].

The Nanoparticle Surface Area Monitor (NSAM) determines the human lung-deposited surface area of particles in units of square micrometers per cubic centimeter (µm^2/cm^3), corresponding to tracheobronchial (TB) and alveolar (A) regions of the lung. The authors have discussed the conceptual limitations of the NSAM and introduced possible extensions for this instrument. They have reported that:

- The NSAM can be used for the measurement of 20 to 400nm particles. It has only been calibrated for spherical particles and it is unclear whether the NSAM can determine the surface area of agglomerates or only of equivalent spheres.
- NSAM can cover a wide range concentration range (very high 10^6 particles/cm^3 to few hundred of particles per cm^3).
- NSAM could be used to obtain the lung deposited surface area concentration in the alveolar, tracheobronchial and nasal regions from a single measurement by means of calibration factors.

Other papers of interest include:

- Ruzer (2008) presented a new method for the measurement of airborne nanoparticle surface area based on the deposition of the "unattached fraction of radon progeny" [21]. Radon progeny consist partly of 1 nm radioactive particles called unattached activity, which have high diffusion coefficients and can be potentially useful as radioactive tracers.

- The Electrical Aerosol Detector (EAD) measures the aerosol diameter concentration as a function of time. *"The aerosol diameter concentration (in mm/cm^3), also called total aerosol length (d1), is defined as the length of a chain with all particles from 1 cm^3 of measured aerosol lined up on the chain. Hence, the EAD measurement falls between number concentration (d0) and surface area (d2)".* Li (2009) proposed to use the EAD TSI Model 3070A as a sizer for nanoparticle size distribution measurement [22].

- Evans (2008) measured ultrafine particle / nanoparticle number and respirable mass concentrations in an automotive grey iron foundry using a particle concentration mapping procedure. One can question therefore whether mapping is an option for nanoparticle measurement in the workplace [23].

- Lall (2008) compared the nanoparticle aggregates volumes determined from the mobility diameter using the idealized aggregate (IA) theory with nanoparticle aggregate volumes determined from the aerosol particle mass analyser (APM) measurements [24]. The APM was used to measure the aggregate mass and calculate the aggregate volume knowing the density of primary particles. The comparison was made for iron oxide and carbon nanoparticle aggregates. In 2006, Lall and Friedlander developed IA calibrations for determining from Differential Mobility Analyzer data aggregates volume distribution if primary particle size is known [25]. The authors confirmed that the IA theory can be used to determine aggregate volume.

1.2.2   Development of compact instruments

There is inadequate portable instrumentation for online personal measurement of nanoparticles exposure. New portable sampling techniques for exposure assessment in the workplace are being developed.

A new miniature electrical aerosol spectrometer (MEAS): Experimental characterization. Ranjan et al (2008) [26]

M Ranjan (2007) designed a compact electrical mobility classification instrument (the miniature electrical mobility aerosol spectrometer) [26]. It is composed of three major parts:
- The inlet
- The electrostatic precipitator (ESP)
- The classifier sections

The particles are charged upstream the instrument with a bipolar or unipolar charger. The particles enter the instrument through the inlet section. The charged particles are

electrostatistically filtered through ESP channels (except 1; the injection channel) and are classified based on their electrical mobility. The charged particles are captured on collection plates connected to electrometers and the signals obtained are used to determine the particle number size distribution of the sampled particles. The performance of the MEAS was experimentally assessed against a SMPS. The authors concluded that:

- The MEAS size distribution measurements closely match commercial size instruments measurements.
- The MEAS detection limit depends on the electrometer characteristics and instrument (prototype) dimension.

They claimed that the miniature MEAS can be used for personal and large scale monitoring for moderate to high particle loading.

Other papers of interest include:

- Qi (2008) have developed and evaluated a prototype low cost miniaturised disk-type electrostatic aerosol precipitator. This prototype could be used in a miniaturised electrical mobility particle sizer as an electrostatic aerosol classifier [27].

- Qi (2008) have developed and experimentally assessed a corona discharge based unipolar mini charger (a non-radioactive charger). It has been designed for the development of portable aerosol sizing instruments based on particle electrical mobility techniques [28].

- Venkatachari (2008) have developed an automated monitor for the continuous sampling of PM 2.5 airborne particles and the measurement of the concentrations of Reactive Oxygen Species (ROS) on the sampled aerosol using dichlorofluorescein (DCFH) fluorescence method. This monitor may also have applicability for the measurement of ROS on engineered airborne nanoparticles and agglomerates in workplaces. ROS (which is a significant component of particle toxicity) is present in the atmosphere on respirable particles [29].

1.2.3 Development of instruments with improved resolution and faster response

CPCs are used to measure number concentration of aerosol particles and can detect submicron particles. Some CPCs can detect particles > 3nm. A paper on a method to improve the particle detection efficiency of Condensation Particle Counters has been published.

Nanometer Particle Detection by the Condensation Particle Counter UF-02proto. Mordas et al (2008) [30].

The authors reported on a method to improve the particle detection efficiency of Condensation Particle Counters (lowest cut size) by increasing the temperature difference between the saturator and the condenser. They found that the cut size D_{50} was 1.8 ± 0.2nm when the temperature difference exceeded 43.5 ^{0}C compared to 4.4nm in the default regime (difference temperature of 32.5 ^{0}C). Further increase in temperature difference did not improve the cut-size.

However with increasing difference temperature, the instrument background caused by homogenous nucleation increases. In the default regime the instrument background is close to zero; at a temperature difference of 43.5 ^{0}C the instrument background was ~ 10 particles / cm^3. The homogenous nucleation process can be prevented using pre-existing aerosol particles in the supersaturated region.

1.2.4 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. A number of papers on the performance, development or improvement of aerosol charger for sizing instruments have been identified. Some papers have also reported the development of charger using low or non-radioactive sources.

- Han (2008) have developed and experimentally assessed a novel high efficiency charger for fine and ultrafine particles. They combined the versatile aerosol concentration enrichment system (VACES) with a unipolar charger using fibre ionizers [31].

- Hontañón (2008) have showed the feasibility of UV photoionization for single unipolar charging of nanoparticles at high flow rates up to 100 l/min. UV photionization could be potentially used as an aerosol charging technique for the commercial production of monodisperse nanoparticles in gas phase by means of electrical mobility analysis [32].

- Maricq (2008) experimentally assessed the bipolar charging efficiency of airborne particles of different morphology (spherical and aggregate particles – oil droplets; flame generated agglomerates; diesel engine exhaust particulate matter) using a tandem Differential Mobility Analyser. Airborne particles were also collected using electrostatic precipitation for Transmission Electron Microscopy image analysis. The authors found consistent charging efficiencies between flame generated and light duty diesel soot. However these aggregate particles showed "small but distinct" differences in charging efficiencies compared to the bipolar charging of spherical oil droplets [33].

- Vivas (2008) have developed and tested a bipolar ionizer, which uses a low level radioactive source of 241 AM (9Bq). The radioactive source has an activity below the exemption limit of the International Atomic Energy Agency (IAEA) [34].

- Han (2008) developed and investigated the performance of a novel unipolar charger using carbon fibre ionizers to charge fine and ultrafine aerosol particles without the generation of ozone. This charger is a non-radioactive charger, which does not require a licence [35].

1.2.5 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.

CPCs are used to measure number concentration of aerosol particles and can detect submicron particles. A paper on the performance of the ultra-fine water based condensation particle counter has been published.

An ultrafine, water-based condensation particle counter and its evaluation under field conditions. Lida et al (2008) [36].

The authors assessed the performance of the TSI 3786 ultrafine water based condensation particle counter (U-WCPC) against the TSI 3025 butanol based ultrafine particle counter for the measurement of ultrafine atmospheric ambient particles under field conditions. The authors found that:

- The response from both instruments agreed to within 5% on average for particles > 5nm.
- At 3nm the particle detection efficiency differed by as much as 30%. This could be due to differences in particle composition and or differences in instrumentation.

A paper on an ultrahigh sensitivity OPC for the measurement of particle >55nm has been identified and is highlighted below.

Performance characteristics of the ultra high sensitivity aerosol spectrometer for particles between 55 and 800nm: Laboratory and field studies. Cai et al (2008) [37].

Optical particle counters (OPCs), which are optical scattering laser based aerosol spectrometers are compact instruments to measure particle number concentration and size distribution but they have poor detection of small particles and a restricted size range. In this paper, the authors report on the experimental assessment of a new optical particle counter, the Particle Metrics Inc., ultra high sensitive aerosol spectrometer (UHSAS) with improved size resolution and detection of small particles for the measurement of particles between 55 and 500nm. The authors found that:

- The number concentration measurement using the UHSAS and condensation particle counter (CPC) agreed well for particles >100nm and number concentration <3000particles/cm^3.
- The UHSAS sized particles with diameter > 55nm within 10% of those measured using a scanning mobility particle sizer (SMPS).
- The detection efficiency considerably decreased for particles <100nm and concentration >3000particles/cm^3.

Myojo (2008) reported on the assessment of several aerosol instruments for the measurement of airborne MWCNTs [38]. The MWCNTs were aerosolised using a Palas RBG-1000 aerosol generator with a two component fluidised bed. The airborne number concentration was monitored using a condensation particle counter (CPC) and the surface area lung deposited particles was measured using a nanoparticle surface area monitor (NSAM). The authors found that the correlation factor between number concentration and surface area (corresponding to the alveolar region) was "almost uniform". The authors found a negative value for the surface area concentration at 0 particle/cm^3.

1.2.6   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. One approach is to collect particles for off-line physical and chemical characterisation using electron microscopy.

The following two papers have been retrieved from the search:
- In a review paper, Park (2008) discussed tandem measurements of airborne submicrometer particles to obtain information on size as well as physico-chemical properties [39].
- Chakrabarty (2008) reported on a novel charge based technique for classifying aspherical fractal-like aerosol agglomerates based on their morphology. This technique could have applications as a morphology classification technique [40].

1.2.7   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. Three papers of interest have been highlighted below.

SiO_2 aerosol nanoparticle reactor for occupational and safety studies. Ostraat et al (2008) [41].

The authors designed and developed a simple reactor to produce stable, well controlled amorphous SiO_2 aerosol nanoparticles of <100nm size at concentrations between ~ 10^4 –10^7 particles/cm^3. The authors reported that this reactor is ideal for:
- inhalation toxicology studies;
- studying the aerosol behaviour of nanoparticles;
- filter, respiratory personal equipment, personal protective equipment, garment efficiency studies;
- developing sampling and monitoring techniques for workplace exposure measurement;
- studying explosion characteristics of aerosol nanoparticles.

Tabrizi (2009) reported on the generation of nanoparticles by microsecond spark discharge evaporation in inert gas. The method can produce separated unagglomerated nanoparticles (3-12nm) or agglomerated nanoparticles depending on the flow rate [42].

Byeon (2008) generated and characterised monometallic aerosol nanoparticles (palladium Pd, platinum Pt, gold Au, silver Ag) as well as bimetallic aerosol nanoparticles (Pd-Pt, Pd-Au, Pd-Ag) using a spark discharge [43].

Hogan (2008) used electrospray processing of ferritin and apoferritin to produce standard size aerosol nanoparticles with different mobility particle diameters for the calibration of aerosol instruments. A furnace aerosol reactor was used after the electrospraying of multi-ferritin complex particles to remove the protein coat and to produce monodisperse iron oxide standard particles (7.9nm in diameter) for the calibration of aerosol instruments as well as colloidal detection instruments or electron microscopes [44].

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).

1.3.1   Engineering control

A paper assessing the effectiveness of a local the effectiveness of a local exhaust ventilation (LEV) unit used during a reactor clean-up operation at a facility where nanomaterials were produced via a gas phase condensation was identified and is highlighted below.

Methner (2008) from NIOSH assessed the effectiveness of a local exhaust ventilation (LEV) unit used during a reactor clean-up operation at a facility where materials (metal oxides nanoparticles e.g. manganese, silver cobalt) were produced via a gas phase condensation at

a rate of one kg per day [8]. The authors found dramatic reduction in emissions with the use of a LEV and the implementation of a more targeted brushing / scraping toward the inlet of the LEV. During reactor cleanout, the mass concentration ranged from 6700 to 710 μg/m^3 without LEV compared to 1700 to 41 μg/m^3 respectively with LEV. The adjusted number concentration ranged from 16917 to 6050 particles/cm3 without LEV compared to 998 to 0 particles/cm^3 with LEV.

Papers proposing or discussing control banding or occupational risk management tools for the control of nanoparticles exposures are now emerging.

Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. Paik et al (2008) [45].

Control banding is a qualitative risk assessment and management approach for controlling workers exposures to chemicals or dust. Paik (2008) developed a pilot control banding tool, which was applied to determine the risk and controls for five operations at two research laboratories [45]. The risk level is determined by a severity score and a probability score. The severity score is based on the surface reactivity, particle shape, particle diameter, solubility, carcinogenicity, reproductive toxicity, mutagenicity, dermal toxicity, toxicity / occupational exposure limit of parent material, carcinogenicity of parent material, reproductive toxicity of parent material, mutagenicity of parent material, dermal hazard potential of parent material. The probability score is based on the estimated amount of nanomaterial, dustiness/mistiness, number of employees with similar exposure, frequency of operation and duration of exposure. The authors found that four of the five operations assessed using the control banding tool had implemented controls with what was recommended by the tool.

Schulte (2008) discussed a conceptual framework for the occupational risk management of engineered nanomaterials including an approach for controlling exposures [46]. The framework takes into account the potential routes of exposure and factors that may influence biological activity and potential toxicity of nanomaterials. It includes approaches based on the hierarchy of controls (elimination or substitution, engineering controls, administrative controls and use of personal protective equipment) as well as those involving health surveillance and medical monitoring.

Also, three papers of interest for this bulletin reviewing the measures to control exposure levels in the workplace and discussing the solutions to handle nanomaterials have been identified:
- In the article *"Health risk versus benefit. Handling with nanomaterials: how safe is safe enough?"* Peter (2007) presented industrial safety recommendations for manufacturers and users [47].
- Hallock (2009) reviewed the potential risk of nanomaterials and discussed the best practices that American Universities have been using to handle nanomaterials (how to prevent / minimise inhalation and dermal exposure, laboratory contamination, exposure during spilling, how to dispose nanomaterials) [48].
- Conti (2008) reported on an international survey of companies or laboratories handling / using or manufacturing nanomaterials about health and safety practices in the workplace [49].

Once can also observe the emergence of papers regarding occupational health surveillance for workers potentially exposed to engineered nanoparticles:
- Schulte (2008) examined the options for occupational health surveillance of workers potentially exposed to engineered nanoparticles [50].

- Nasterlack (2008) discussed the considerations on occupational medical surveillance in employees handling nanoparticles. They recommended the establishment of exposure registries for future epidemiologic studies [51].
- NIOSH (2009) has published an *"Interim Guidance for Medical Screening and Hazard Surveillance for Workers Potentially Exposed to Engineered Nanoparticles"* [52]. In this report, NIOSH recommended:
  - "To take prudent measures to control exposures to engineered nanoparticles".
  - "To conduct hazard surveillance as the basis for implementing controls".
  - "To continue using established medical surveillance approaches".
  - NIOSH says that there is insignificant evidence to recommend specific medical screening of workers exposed to engineered nanoparticles.

1.3.2   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. Several papers on the performance of filters have been published. It is also important that the degree of face-seal leakage, while the user is wearing the RPE, is assessed. For the first time, the search has retrieved a paper on the performance of disposable respirators worn by a human subject during exercises and is highlighted below.

Respiratory Performance Offered by N95 Respirators and Surgical Masks: Human Subject Evaluation with NaCl Aerosol Representing Bacterial and Viral Particle Size Range. Lee et al (2008) [53].

The authors assessed the performance of four N95 facepieces worn by a human subject during exercises (OSHA fit testing exercise) using NaCl (aerodynamic size = 0.04-1.3 μm) in a test chamber. The particle size selective number concentrations outside and inside the respirator were measured using an ELPI (Electrical Low Pressure Impactor). The authors found that:
- 29% of N95 respirators had protection factors>10;
- The minimum protection factors were observed in the size range of 40-200nm.
- No significant differences were found regarding protection factors between N95 respirator with and without an exhalation valve.

Several papers on the performance of filters have been published and are presented below.

Filter Performance of N99 and N95 Facepiece Respirators Against Viruses and Ultrafine Particles. Eninger et al (2008) [54].

The authors assessed the performance of two N99 and one N95 face respirators using NaCl aerosol (20-500nm particle size) and a manikin based protocol with the respirators sealed on the manikin. Three inhalation flow rates were tested: 30, 85 and 150l/min. The authors found that:
- The particle penetration increases with increasing flow rates.
- The Most Penetrating Particle Size (MPPS) was <0.1 μm.
- Peak penetrations for N99 model A were 10.2% (at 150l/min), 5.9% (85l/min), 1.3% (30l/min). Mean penetration was 3.2% (85l/min) for all particle sizes from 20 to 500nm.
- Peak penetrations for N99 model B were 6.6% (at 150l/min), 4.3% (85l/min), 1% (30l/min). Mean penetration was 2.4% (85l/min) for all particle sizes from 20 to 500nm.
- Peak penetrations for N95 were 8.1% (at 150l/min), 4.8% (85l/min), 1.4% (30l/min). Mean penetration was 2.9% (85l/min) for all particle sizes from 20 to 500nm.

The penetration is defined as:
C_{down} (challenge aerosol concentration downstream of respirator filter) / C_{up} (aerosol concentration upstream) x 100%

Filter efficiency as a function of nanoparticle velocity and shape. Boskovic et al (2008) [55].

The authors have experimentally investigated the influence of the filtration velocity on the filter efficiency for particles of different shapes (spherical, cubic and cubic with rounded edges). The authors found that:
- The shape of particles plays a significant role in the filter filtration at the velocity of 5cm/s.
- At the velocity of 10-20 cm/s, the shape of the particles plays a less important role as inertial removal mechanism is becoming more important.

Evaluation of the effect of media velocity on filter efficiency and most penetrating particle size of nuclear grade high-efficiency particulate air filters. Alderman (2008) [56].

The authors assessed the collection efficiency of nuclear grade HEPA filters as a function of media velocity (from 2.0 to 4.5 cm/s) using a potassium chloride aerosol having a particle size distribution centered near the HEPA filter most penetrating particle size. The authors found that in this study:
- The filter efficiency of nuclear grade filters at the onset of aerosol decreased with increasing media velocity but ranged from 99.999% to 99.977%.
- The most penetrating particle size decreased slightly as media velocity increased and was 110-130nm.

Also of interest on the performance of filters, the search identified the following papers:

- Steffens (2007) assessed the collection efficiency of a HEPA cellulose fibre filter and a polyester fibre filter using a monodipersed sodium chloride aerosol (particle sizes ranging from 8.5 to 94.8nm). The characteristics of the HEPA cellulose fibre filter were: porosity of 0.92, 0.4 mm thick and 0.45μm fibre median diameter. The characteristics of the polyester fibre filter were: porosity of 0.882, 4.5 mm thick and 16μm fibre median diameter. The tests were performed at gas superficial velocities of 0.03 to 0.25 m/s. The authors found that the collection efficiency of the filter decreased with increasing particle size and it also decreased with increasing filtration velocity [57] [58].

- Wang (2008) experimentally assessed the performance of filters composed of a layer of nanofibres (diameter of ~ 0.15 μm) on a substrate made of microfibres using 20-78 nm particles [59]. The authors found that:
    - The filtration efficiency and the pressure drop increase as the nanofibre solidity increases
    - The nanofibre filters have a better figure of merit for particles >100nm compared to conventional fibreglass filters
    - The nanofibre filters do not have a better figure of merit for particles <100nm compared to conventional fibreglass filters
  The figure of merit is the ratio between the filtration efficiency and the pressure drop.

- Shin (2008) experimentally studied single fibre collection efficiency for a stainless steel screen mesh at temperature up to 500K for monodisperse silver nanoparticles in the size

range from 3 to 20nm [60]. Ceramic and metallic media have been used for particle filtration at elevated temperature. The authors found that:
  - No thermal rebound was detected even at 500K for 3nm diameter particles.
  - Single fibre efficiency increased by about 8% for particles of size 3; 4 and 5 nm for a 250K temperature increase at fixed mass flow rate.

- Eninger (2008) evaluated whether the protocols used in the USA to certify respirator filters for non-nanoparticles are useful to assess filter penetration for nanoparticles. The authors found that the sodium chloride and dioctylphthalate aerosols employed to certify respirator filters contain a significant fraction of particles < 100nm. However the photometric method in the certification test is not capable of measuring light scattered by particles smaller than about 100nm [61].

A number of papers presenting numerical or mathematical models have been also published including:
- Podgórski (2009) reported a mathematical model (fully segregated flow model) to predict the upper limit of aerosol nanoparticles penetration through inhomogeneous fibrous filters [62].
- Prsekop (2008) used a mathematical model for the calculation of the filtration efficiency of bilayer filter structures composed of microfibres and a non-uniformed distribution of nanofibres for the removal of nanoparticles [63].
- Wang (2009) presented a numeral study of the filtration of aerosol particles by elliptical fibres [64].

1.4   Characterisation

1.4.1   Characterisation of bulk nanomaterials

1.4.2   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. Few papers addressing these issues on the generation of nanoparticles for toxicology studies have been published:

- Baron (2008) developed a generation system to produce respirable aerosol from very low density HiPCO SWCNTs for animal inhalation exposure experiments [65].

- Ku (2009) presented a method to generate single-wall carbon nanotube aerosol using capillary electrospray of aqueous suspensions. Monodisperse SWCNT aerosol <100nm (mainly non-agglomerated single fibres) as well as polydiperse aerosol >100nm (ribbon shape and long straight fibres) were generated from this method [66].

- Ostraat (2008) designed and developed a simple reactor to produce stable, well controlled amorphous SiO_2 aerosol nanoparticles of <100nm size at concentrations between ~ 10^4 –10^7 particles/cm^3 [41].

Also of interest are the papers from Savi (2008) and Stevens (2008):
- Savi (2008) presented a deposition chamber to expose lung cells to nanoparticles with a reproducible and uniform deposition close to the particle deposition conditions in the lung [67].

- Stevens (2008) presented "A new method for quantifiable and controlled dosage of particulate matter for in vitro studies: the electrostatic particulate dosage and exposure system (EPDExS)" [68].

1.4.3   Characterisation of nanoparticles in their bulk form, in fluids or in biological tissues

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.

In a short article **"How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization?" Warheit (2008) [69].**

Warheit recommends a minimum of set of characterisation:
- Particle size and size distribution (wet state) and surface area (dry state) in the relevant media being used (which will depend on the route of exposure);
- Crystal structure and crystallinity;
- Aggregation state (in the relevant media);
- Composition and surface coatings;
- Surface reactivity;
- Synthesis or preparation method as well as any postsynthetic modifications;
- Purity of the sample.

Reactivity of engineered inorganic nanoparticles and carbon nanostructures in biological media. Bastus et al (2008) [70].

The authors reviewed from the literature the physico-chemical properties of engineered inorganic nanoparticles and carbon nanostructures that makes them potentially more hazardous based on their reactivity in biological media. The authors focussed on the following parameters: particle size, particle shape, particle surface, particle concentration, particle composition and structure. They concluded that: In terms of reactivity of nanoparticles in biological media, the following should be taken into account:
- The potential degradation of the nanoparticles inorganic core;
- The surface: molecule presence, substitution and release
- The coating molecule reactivity
- Nanoparticles stability and agglomeration
- Nanoparticles translocation and internalisation in cells.

1.4.4   Characterisation of nanoparticles in their bulk form, in fluids or in biological tissues

Microscopy is an important tool for characterisation especially to localise nanoparticles in tissues and cells and to better understand how nanoparticles enter cells and their fate after uptake. Two papers have been selected for this bulletin:

- Bussy (2008) used X-Ray fluorescence microscopy (micro XRF) to study macrophages exposed to carbon nanotubes. Using elemental mapping, CNTs were localised within

cells (iron was used as a nanotube tracer as iron particles are found inside or bound to CNTs). Chemical modifications of the cells were detected after CNTs internalization [71].

- Sahin (2008)presented the scanning near-field ultrasonic holography technique, which can be used to image nanoparticles buried below the cell surfaces [72].

- Tetard (2008) used scanning near-field ultrasonic holography to detect nanoparticles inside cells taken from the lungs of mice that have been exposed to nanohorns [73].

In previous bulletins, a number of papers on the quantitative detection of nanoparticles in tissues and organs of animals after exposure to nanoparticles have been reported. In this search, a paper reporting on a rapid method for the characterisation, separation and quantification of inorganic nanoparticles from cells based on sedimentation field-flow fractionation and light scattering detection has been retrieved [74].

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 searches identified several papers reporting on dispersion media and techniques to characterise nanoparticle agglomeration in solution, including:

- Jiang (2009) reported on the characterisation of size, surface charge and agglomeration state of nanoparticle dispersions for toxicological studies [75]. The authors investigated the stability of the dispersions using a method based on different ultrasonication techniques (bath and probe). This method was developed to distinguish agglomerates from aggregates (strong bonds), and to estimate the extent of particle agglomeration. They found that probe ultrasonication performed better than bath ultrasonication in dispersing TiO_2 agglomerates when the stabilizing agent sodium pyrophosphate was used. They used two types of TiO_2 nanoparticles to demonstrate the identification of aggregated and agglomerated samples.

- Schulze (2008) reported on the characterisation of the interaction of nanoparticles with physiological media (proteins) for in vitro toxicology experiments and discussed pitfalls when dispersing nanoparticles in physiological media. The authors also warn about microbial contaminant and the need to sterilize using γ irradiation dispersed and powder nanoparticles for the use in physiological media [76].

- Murdock (2008) reported on the investigation of the size distribution, state of agglomeration and zeta potential of a range of various nanoparticles dispersed in water and cell culture media with and without serum using DLS [77]. The authors found that in general:
  - Many metals and metal oxide nanomaterials agglomerate in solution. The size of the agglomerates in cell culture decreased when serum was added possibly because of the interaction between the particles and serum proteins.
  - Sonication slightly reduced agglomeration and has minimal effect on particle surface charge.
  - Stock solutions of nanoparticles for toxicological studies significantly changed in terms of particle agglomeration and surface charge overtime.

- Kozan (2008) investigated the dispersion stability of WO_3 nanoparticles and nanowires in various solvents using small angle static light scattering and elliptically polarized light scattering (EPLS) techniques [78].

- Hasellöv (2008) discussed methods for the analysis and characterisation of nanoparticles in environmental matrices (e.g. water, soil, sediment, sewage, sludge and biological specimens). This paper focuses on "mature and validated methods" [79].

Dynamic Light Scattering (DLS) is used to measure the hydrodynamic sizes, polydispersities and agglomeration /aggregation of nanoparticles in liquid. Kaszuba (2008) investigated the lower size limit of detection of DLS using sucrose as a test sample [80]. DLS measures time dependent fluctuations in the intensity of the scattered light from particles undergoing Brownian motion. The hydrodynamic diameter of particles in liquid can be obtained from these fluctuations. The authors found that hydrodynamic diameter values of <1nm can be obtained by the use of 173^0 backscatter detection in combination with fibre optics.

Two papers on the bulk material characterisation of carbon nanotubes have been identified and are summarised below:

- Plata (2008) reported on the elemental, molecular and stable carbon isotope composition of commercial purified and unpurified SWCNTs [81]. Analysis of metal, metalloid and rare earth elements using inductively coupled plasma mass spectrometry (ICPMS) in the samples were carried out. The SWCNTs contained metals used as catalysts in their syntheses at weight 1.3 - 29% (14-29% for unpurified SWCNTs and 1.3 - 4.1% for purified SWCNTs). Purified SWCNTs also contained unexpected metals (Cr, Cu, Pb at 0.01-0.03 ppt). The total carbon and nitrogen content of SWCNTs were determined using an Elementar CHN analyzer. The samples content contained up to 0.48% nitrogen. The total carbon ranged from 60 to 97%. The amorphous carbon content (determined using thermogravimetric analysis) accounted for up to 45% of the material mass. The samples contained less than 5% of toluene extractable materials (determined by GCMS).

- Trigueiro (2007) used conventional and high resolution thermogravimetry to quantify the different fractions of carbonaceous and metallic materials in carbon nanotubes [82].

Other papers of interest on bulk material characterisation include:

- Ahrenkiel (2008) used tomographic reconstruction by transmission electron microscopy to obtain the three-dimensional shape of nanoparticle and their crystal structure [83].
- Fenoglio (2008) used a range of analytical techniques to detect in carbon nanotubes the presence of defects, metals and oxygenated functionalities including micro-Raman spectroscopy, adsorption calorimetry, X-ray photoelectron spectroscopy, inductively coupled plasma mass spectrometry, and atomic emission spectroscopy [84]. Furthermore, the potential of the modified CNT to scavenge hydroxyl radicals was evaluated using electron spin resonance spectroscopy (spin trapping).

1.5   Bibliography of key papers

1.   Fujitani, Y., and Hirano, S. (2008). [health effects of nanoparticles and nanomaterials (ii) methods for measurement of nanoparticles and their presence in the air]. *Nippon Eiseigaku Zasshi* **63,** 663-9.

2.   Han, J. H., Lee, E. J., Lee, J. H., So, K. P., Lee, Y. H., Bae, G. N., Lee, S. B., Ji, J. H., Cho, M. H., and Yu, I. J. (2008). Monitoring multiwalled carbon nanotube exposure in carbon nanotube research facility. *Inhal Toxicol* **20,** 741-9.

3.   Bello, D., Wardle, B., Yamamoto, N., Guzman deVilloria, R., Garcia, E., Hart, A., Ahn, K., Ellenbecker, M., and Hallock, M. (2009). Exposure to nanoscale particles and fibers during machining of hybrid advanced composites containing carbon nanotubes. *Journal of Nanoparticle Research* **11** 231-249.

4.   Bello, D., Hart, A. J., Ahn, K., Hallock, M., Yamamoto, N., Garcia, E. J., Ellenbecker, M. J., and Wardle, B. L. (2008). Particle exposure levels during cvd growth and subsequent handling of vertically-aligned carbon nanotube films. *Carbon* **46,** 974-977.

5.   Fujitani, Y., Kobayashi, T., Arashidani, K., Kunugita, N., and Suemura, K. (2008). Measurement of the physical properties of aerosols in a fullerene factory for inhalation exposure assessment. *J Occup Environ Hyg* **5,** 380-9.

6.   Yeganeh, B., Kull, C. M., Hull, M. S., and Marr, L. C. (2008). Characterization of airborne particles during production of carbonaceous nanomaterials. *Environ Sci Technol* **42,** 4600-6.

7.   Tsai, S.-J., Ada, E., Isaacs, J., and Ellenbecker, M. (2009). Airborne nanoparticle exposures associated with the manual handling of nanoalumina and nanosilver in fume hoods. *Journal of Nanoparticle Research* **11** 147-161.

8.   Methner, M. M. (2008). Engineering case reports. Effectiveness of local exhaust ventilation (lev) in controlling engineered nanomaterial emissions during reactor cleanout operations. *J Occup Environ Hyg* **5,** D63-9.

9.   Demou, E., Peter, P., and Hellweg, S. (2008). Exposure to manufactured nanostructured particles in an industrial pilot plant. *Ann Occup Hyg* **52,** 695-706.

10.   Park, B., Donaldson, K., Duffin, R., Tran, L., Kelly, F., Mudway, I., Morin, J. P., Guest, R., Jenkinson, P., Samaras, Z., Giannouli, M., Kouridis, H., and Martin, P. (2008). Hazard and risk assessment of a nanoparticulate cerium oxide-based diesel fuel additive - a case study. *Inhal Toxicol* **20,** 547-66.

11.   Schmid, K., and Riediker, M. (2008). Use of nanoparticles in swiss industry: A targeted survey. *Environ Sci Technol* **42,** 2253-60.

12.   Liao, C.-M., Chiang, Y.-H., and Chio, C.-P. (2009). Assessing the airborne titanium dioxide nanoparticle-related exposure hazard at workplace. *Journal of Hazardous Materials* **162,** 57-65.

13.   Liao, C.-M., Chiang, Y.-H., and Chio, C.-P. (2008). Model-based assessment for human inhalation exposure risk to airborne nano/fine titanium dioxide particles. *Science of The Total Environment* **407,** 165-177.

14.   Cheng, Y. H., Chao, Y. C., Wu, C. H., Tsai, C. J., Uang, S. N., and Shih, T. S. (2008). Measurements of ultrafine particle concentrations and size distribution in an iron foundry. *J Hazard Mater* **158,** 124-30.

15.   European Committee for Standardization. (2006). EN 15051 Workplace atmospheres—measurement of the dustiness of bulk materials—requirements and reference test methods. *Berlin: Beauth Verlag.*

16.   Jensen, K., Koponen, I., Clausen, P., and Schneider, T. (2008). Dustiness behaviour of loose and compacted bentonite and organoclay powders: What is the difference in exposure risk? *Journal of Nanoparticle Research* **11,** 133-146.

17.   Tsai, C.-J., Wu, C.-H., Leu, M.-L., Chen, S.-C., Huang, C.-Y., Tsai, P.-J., and Ko, F.-H. (2009). Dustiness test of nanopowders using a standard rotating drum with a modified sampling train. *Journal of Nanoparticle Research* **11,** 121-131.

18.   Schwager, T., Wolf, D. E., and Poschel, T. (2008). Fractal substructure of a nanopowder. *Phys Rev Lett* **100,** 218002.

19.   Seipenbusch, M., Binder, A., and Kasper, G. (2008). Temporal evolution of nanoparticle aerosols in workplace exposure. *Ann Occup Hyg* **52,** 707-16.

20.   Asbach, C., Fissan, H., Stahlmecke, B., Kuhlbusch, T., and Pui, D. (2009). Conceptual limitations and extensions of lung-deposited nanoparticle surface area monitor (nsam). *Journal of Nanoparticle Research* **11,** 101-109, .

21.   Ruzer, L. (2008). Assessment of nanoparticle surface area by measuring unattached fraction of radon progeny. *Journal of Nanoparticle Research* **10,** 761-766.

22.   Li, L., Chen, D.-R., and Tsai, P.-J. (2009). Use of an electrical aerosol detector (ead) for nanoparticle size distribution measurement. *Journal of Nanoparticle Research* **11,** 111-120.

23.   Evans, D. E., Heitbrink, W. A., Slavin, T. J., and Peters, T. M. (2008). Ultrafine and respirable particles in an automotive grey iron foundry. *Ann Occup Hyg* **52,** 9-21.

24.   Lall, A. A., Rong, W., Mädler, L., and Friedlander, S. K. (2008). Nanoparticle aggregate volume determination by electrical mobility analysis: Test of idealized aggregate theory using aerosol particle mass analyzer measurements. *Journal of Aerosol Science* **39,** 403-417.

25.   Lall, A. A., and Friedlander, S. K. (2006). On-line measurement of ultrafine aggregate surface area and volume distributions by electrical mobility analysis: I. Theoretical analysis. *Journal of Aerosol Science* **37,** 260-271.

26.   Ranjan, M., and Dhaniyala, S. (2008). A new miniature electrical aerosol spectrometer (meas): Experimental characterization. *Journal of Aerosol Science* **39,** 710-722.

27.   Qi, C., Chen, D.-R., and Greenberg, P. (2008). Fundamental study of a miniaturized disk-type electrostatic aerosol precipitator for a personal nanoparticle sizer. *Aerosol Science and Technology* **42,** 505-512.

28.   Qi, C., Chen, D.-R., and Greenberg, P. (2008). Performance study of a unipolar aerosol mini-charger for a personal nanoparticle sizer. *Journal of Aerosol Science* **39,** 450-459.

29.   Venkatachari, P., and Hopke, P. K. (2008). Development and laboratory testing of an automated monitor for the measurement of atmospheric particle-bound reactive oxygen species (ros). *Aerosol Science and Technology* **42,** 629 - 635.

30.   Mordas, G., Sipilä, M., and Kulmala, M. (2008). Nanometer particle detection by the condensation particle counter uf-02proto. *Aerosol Science and Technology* **42,** 521 - 527.

31.   Han, B., Hudda, N., Ning, Z., and Sioutas, C. (2008). Enhanced unipolar charging of concentration-enriched particles using water-based condensational growth. *Journal of Aerosol Science* **39,** 770-784.

32.   Hontanon, E., and Kruis, F. E. (2008). Single charging of nanoparticles by uv photoionization at high flow rates. *Aerosol Science and Technology* **42,** 310-323.

33.   Maricq, M. M. (2008). Bipolar diffusion charging of soot aggregates. *Aerosol Science and Technology* **42,** 247-254.

34.   Vivas, M. M., Hontañón, E., and Schmidt-Ott, A. (2008). Design and evaluation of a low-level radioactive aerosol charger based on 241am. *Journal of Aerosol Science* **39,** 191-210.

35.   Han, B., Kim, H.-J., Kim, Y.-J., and Sioutas, C. (2008). Unipolar charging of fine and ultra-fine particles using carbon fiber ionizers. *Aerosol Science and Technology* **42,** 793 - 800.

36.   Lida, K., Stolzenburg, M. R., McMurry, P. H., Smith, J. N., Quant, F. R., Oberreit, D. R., Keady, P. B., Eiguren-Fernandez, A., Lewis, G. S., Kreisberg, N. M., and Hering, S. V. (2008). An ultrafine, water-based condensation particle counter and its evaluation under field conditions. *Aerosol Science and Technology* **42,** 862 - 871.

37.   Cai, Y., Montague, D. C., Mooiweer-Bryan, W., and Deshler, T. (2008). Performance characteristics of the ultra high sensitivity aerosol spectrometer for particles between 55 and 800 nm: Laboratory and field studies. *Journal of Aerosol Science* **39,** 759-769.

38.   Myojo, T., Oyabu, T., Nishi, K., Kadoya, C., Tanaka, I., Ono-Ogasawara, M., Sakae, H., and Shirai, T. (2008). Aerosol generation and measurement of multi-wall carbon nanotubes. *Journal of Nanoparticle Research*.

39.   Park, K., Dutcher, D., Emery, M., Pagels, J., Sakurai, H., Scheckman, J., Qian, S., Stolzenburg, M. R., Wang, X., Yang, J., and McMurry, P. H. (2008). Tandem measurements of aerosol properties. A review of mobility techniques with extensions. *Aerosol Science and Technology* **42,** 801 - 816.

40.   Chakrabarty, R. K., Moosmüller, H., Garro, M. A., Patrick Arnott, W., Slowik, J. G., Cross, E. S., Han, J.-H., Davidovits, P., Onasch, T. B., and Worsnop, D. R. (2008). Morphology based particle segregation by electrostatic charge. *Journal of Aerosol Science* **39,** 785-792.

41.   Ostraat, M. L., Swain, K. A., and Krajewski, J. J. (2008). Sio2 aerosol nanoparticle reactor for occupational health and safety studies. *J Occup Environ Hyg* **5,** 390-8.

42.   Tabrizi, N., Ullmann, M., Vons, V., Lafont, U., and Schmidt-Ott, A. (2009). Generation of nanoparticles by spark discharge. *Journal of Nanoparticle Research* **11,** 315-332.

43.   Byeon, J. H., Park, J. H., and Hwang, J. (2008). Spark generation of monometallic and bimetallic aerosol nanoparticles. *Journal of Aerosol Science* **39,** 888-896.

44.   J. Hogan Jr, C., and Biswas, P. (2008). Narrow size distribution nanoparticle production by electrospray processing of ferritin. *Journal of Aerosol Science* **39,** 432-440.

45.   Paik, S. Y., Zalk, D. M., and Swuste, P. (2008). Application of a pilot control banding tool for risk level assessment and control of nanoparticle exposures. *Ann Occup Hyg* **52,** 419-28.

46.   Schulte, P., Geraci, C., Zumwalde, R., Hoover, M., and Kuempel, E. (2008). Occupational risk management of engineered nanoparticles. *Journal of Occupational and Environmental Hygiene* **5,** 239 - 249.

47.   Peter, T., and Mertsching, H. (2007). Health risk versus benefit: Handling with nanomaterials: How safe - is safe enough? *NanoS* **3,** 4-8.

48.   Hallock, M. F., Greenley, P., DiBerardinis, L., and Kallin, D. (2009). Potential risks of nanomaterials and how to safely handle materials of uncertain toxicity. *Journal of Chemical Health and Safety* **16,** 16-23.

49.   Conti, J. A., Killpack, K., Gerritzen, G., Huang, L., Mircheva, M., Delmas, M., Harthorn, B. H., Appelbaum, R. P., and Holden, P. A. (2008). Health and safety practices in the nanomaterials workplace: Results from an international survey. *Environ Sci Technol* **42,** 3155-62.

50.   Schulte, P. A., Trout, D., Zumwalde, R. D., Kuempel, E., Geraci, C. L., Castranova, V., Mundt, D. J., Mundt, K. A., and Halperin, W. E. (2008). Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: State of the science. *J Occup Environ Med* **50,** 517-26.

51.   Nasterlack, M., Zober, A., and Oberlinner, C. (2008). Considerations on occupational medical surveillance in employees handling nanoparticles. *International Archives of Occupational and Environmental Health* **81,** 721-726.

52.   NIOSH, Dept of Health and Human Sevices. (2009). Current intelligence bulletin 60. Interim guidance for medical screening and hazard surveillance for workers potentially exposed to engineered nanoparticles. **2009-116**.

53.   Lee, S.-A., Grinshpun, S. A., and Reponen, T. (2008). Respiratory performance offered by n95 respirators and surgical masks: Human subject evaluation with nacl aerosol representing bacterial and viral particle size range. *Ann Occup Hyg* **52,** 177-185.

54.   Eninger, R. M., Honda, T., Adhikari, A., Heinonen-Tanski, H., Reponen, T., and Grinshpun, S. A. (2008). Filter performance of n99 and n95 facepiece respirators against viruses and ultrafine particles. *Ann Occup Hyg* **52,** 385-396.

55.   Boskovic, L., Agranovski, I. E., Altman, I. S., and Braddock, R. D. (2008). Filter efficiency as a function of nanoparticle velocity and shape. *Journal of Aerosol Science* **39,** 635-644.

56.   Alderman, S. L., Parsons, M. S., Hogancamp, K. U., and Waggoner, C. A. (2008). Evaluation of the effect of media velocity on filter efficiency and most penetrating particle size of nuclear grade high-efficiency particulate air filters. *J Occup Environ Hyg* **5,** 713-20.

57.   Steffens, J., and Coury, J. R. (2007). Collection efficiency of fiber filters operating on the removal of nano-sized aerosol particles: I--homogeneous fibers. *Separation and Purification Technology* **58,** 99-105.

58.   Steffens, J., and Coury, J. R. (2007). Collection efficiency of fiber filters operating on the removal of nano-sized aerosol particles: II. Heterogeneous fibers. *Separation and Purification Technology* **58,** 106-112.

59.   Wang, J., Kim, S. C., and Pui, D. Y. H. (2008). Investigation of the figure of merit for filters with a single nanofiber layer on a substrate. *Journal of Aerosol Science* **39,** 323-334.

60.   Shin, W. G., Mulholland, G. W., Kim, S. C., and Pui, D. Y. H. (2008). Experimental study of filtration efficiency of nanoparticles below 20 nm at elevated temperatures. *Journal of Aerosol Science* **39,** 488-499.

61.   Eninger, R. M., Honda, T., Reponen, T., McKay, R., and Grinshpun, S. A. (2008). What does respirator certification tell us about filtration of ultrafine particles? *Journal of Occupational and Environmental Hygiene* **5,** 286 - 295.

62.   Podgórski, A. (2009). Estimation of the upper limit of aerosol nanoparticles penetration through inhomogeneous fibrous filters. *Journal of Nanoparticle Research* **11,** 197-207.

63.   Przekop, R., and GradoÅ„, L. (2008). Deposition and filtration of nanoparticles in the composites of nano- and microsized fibers. *Aerosol Science and Technology* **42,** 483 - 493.

64.   Wang, J., and Pui, D. (2009). Filtration of aerosol particles by elliptical fibers: A numerical study. *Journal of Nanoparticle Research* **11,** 185-196.

65.   Baron, P. A., Deye, G. J., Chen, B. T., Schwegler-Berry, D. E., Shvedova, A. A., and Castranova, V. (2008). Aerosolization of single-walled carbon nanotubes for an inhalation study. *Inhalation Toxicology* **20,** 751-760.

66.   Ku, B., and Kulkarni, P. (2009). Morphology of single-wall carbon nanotube aggregates generated by electrospray of aqueous suspensions. *Journal of Nanoparticle Research* **11,** 1393-1403.

67.   Savi, M., Kalberer, M., Lang, D., Ryser, M., Fierz, M., Gaschen, A., Ricka, J., and Geiser, M. (2008). A novel exposure system for the efficient and controlled deposition of aerosol particles onto cell cultures. *Environ Sci Technol* **42,** 5667-74.

68.   Stevens, J. P., Zahardis, J., MacPherson, M., Mossman, B. T., and Petrucci, G. A. (2008). A new method for quantifiable and controlled dosage of particulate matter for in vitro studies: The electrostatic particulate dosage and exposure system (epdexs). *Toxicol In Vitro* **22,** 1768-74.

69.   Warheit, D. B. (2008). How meaningful are the results of nanotoxicity studies in the absence of adequate material characterization? *Toxicol Sci* **101,** 183-5.

70.   Bastus, N. G., Casals, E., Vazquez-Campos, S., and Puntes, V. (2008). Reactivity of engineered inorganic nanoparticles and carbon nanostructures in biological media. *Nanotoxicology* **2,** 99-112.

71.   Bussy, C., Cambedouzou, J., Lanone, S., Leccia, E., Heresanu, V., Pinault, M., Mayne-L'hermite, M., Brun, N., Mory, C., Cotte, M., Doucet, J., Boczkowski, J., and Launois, P. (2008). Carbon nanotubes in macrophages: Imaging and chemical analysis by x-ray fluorescence microscopy. *Nano Lett* **8,** 2659-63.

72.   Sahin, O. (2008). Probe microscopy: Scanning below the cell surface *Nature Nanotechnology* **3,** 461-462.

73.   Tetard, L., Passian, A., Venmar, K. T., Lynch, R. M., Voy, B. H., Shekhawat, G., Dravid, V. P., and Thundat, T. (2008). Imaging nanoparticles in cells by nanomechanical holography. *Nat Nano* **3,** 501-505.

74.   Tadjiki, S., Assemi, S., Deering, C., Veranth, J., and Miller, J. (2008). Detection, separation, and quantification of unlabeled silica nanoparticles in biological media using sedimentation field-flow fractionation. *Journal of Nanoparticle Research* **10.1007/s11051-008-9560-3**.

75.   Jiang, J., Oberdörster, G., and Biswas, P. (2009). Characterization of size, surface charge, and agglomeration state of nanoparticle dispersions for toxicological studies. *Journal of Nanoparticle Research* **11,** 77-89.

76.   Schulze, C., Kroll, A., Lehr, C.-M., Schafer, U. F., Becker, K., Schnekenburger, J., Schulze Isfort, C., Landsiedel, R., and Wohlleben, W. (2008). Not ready to use - overcoming pitfalls when dispersing nanoparticles in physiological media. *Nanotoxicology* **2,** 51-61.

77.   Murdock RC, Braydich-Stolle L, Schrand AM, Schlager JJ, and SM, H. (2008). Characterization of nanomaterial dispersion in solution prior to in vitro exposure using dynamic light scattering technique. *Toxicol Sci* **101,** 239-253.

78.   Kozan, M., Thangala, J., Bogale, R., Mengüç, M., and Sunkara, M. (2008). In-situ characterization of dispersion stability of wo3 nanoparticles and nanowires. *Journal of Nanoparticle Research* **10,** 599-612.

79.   Hassellöv, M., Readman, J., Ranville, J., and Tiede, K. (2008). Nanoparticle analysis and characterization methodologies in environmental risk assessment of engineered nanoparticles. *Ecotoxicology* **17,** 344-361.

80.   Kaszuba, M., McKnight, D., Connah, M., McNeil-Watson, F., and Nobbmann, U. (2008). Measuring sub nanometre sizes using dynamic light scattering. *Journal of Nanoparticle Research* **10,** 823-829.

81.   Plata, D. L., Gschwend, P. M., and Reddy, C. M. (2008). Industrially synthesized single-walled carbon nanotubes: Compositional data for users, environmental risk assessments, and source apportionment. *Nanotechnology* **19,** 185706

82.   Trigueiro, J. P. C., Silva, G. G., Lavall, R. L., Furtado, C. A., Oliveira, S., Ferlauto, A. S., Lacerda, R. G., Ladeira, L. O., Liu, J.-W., Frost, R. L., George, G. A. (2007). Purity evaluation of carbon nanotube materials by thermogravimetric, TEM, and SEM methods *Journal of Nanoscience and Nanotechnology* **7,** 3477-3486.

83.   Ahrenkiel, S. P., Yu, P. R., Murphy, J. E., NedeljkoviĆ, J. M., and Donohoe, B. S. (2008). Nanoparticle shape and configuration analysis by transmission electron tomography. *Journal of Microscopy* **230,** 382-387.

84.   Fenoglio, I., Greco, G., Tomatis, M., Muller, J., Raymundo-Pinero, E., Beguin, F., Fonseca, A., Nagy, J. B., Lison, D., and Fubini, B. (2008). Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: Physicochemical aspects. *Chem Res Toxicol* **21,** 1690-7.

2. HEALTH EFFECTS

The publications retrieved by the health effects searches in the ten months from March 2008 to December 2008 showed a broadly similar pattern of distribution amongst the different topics to previous bulletins. Very few publications were identified in the searches on ambient nanoparticles and these have only been included in this bulletin when the results are pertinent for occupational exposure to engineered nanomaterials. Approximately equal numbers of papers described the effects of engineered nanoparticles in animal (*in vivo*) and cellular (*in vitro*) systems (Figure 2), whereas in previous bulletins, the proportion of cellular study reports was greater than the number of animal studies. A large number of reviews was retrieved by the health effects searches for this period, but the proportion of this type of article compared to the other types retrieved was lower than in previous bulletins (27% versus >50%).
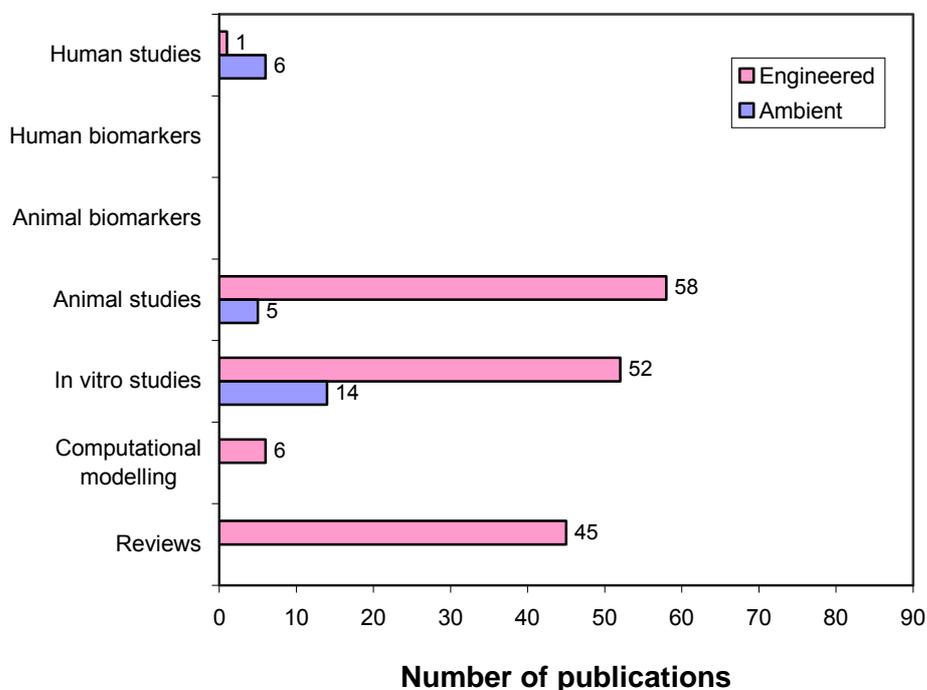

Figure 2: Breakdown per topic of the numbers of publications retrieved in the 10 months from March 2008 to December 2008 on the human health effects of *engineered* nanoparticles.

2.1 Human studies and epidemiology

Seven publications were identified in the searches that reported the effects of nanoparticles in humans. One of these considered dermal exposure to engineered nanomaterials:

Imaging of zinc oxide nanoparticle penetration in human skin *in vitro* and *in vivo*. Zvyagin et al (2008) [1]

The distribution of topically applied nano-ZnO (18 nm) in excised and *in vivo* human skin was analysed using multi-photon microscopy imaging in combination with scanning electron microscopy and an energy-dispersive x-ray technique to determine the extent of penetration of nanoparticles into the sub-dermal layers of human skin. *In vivo*, the ZnO nanoparticles stayed in the stratum corneum, accumulating in skin folds and/or hair follicles.

One paper investigated the toxicokinetics of ultrafine carbon nanoparticles following inhalation:

Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. Moller et al (2008) [2]

Technetium ^{99}Tc-labelled carbon nanoparticles (100 nm) were inhaled by healthy non-smokers, asymptomatic smokers or patients with chronic obstructive pulmonary disease using a bolus inhalation technique. Retention, clearance and translocation were measured by radiotracer imaging. Particle retention (75-96%) in the lung was not affected by smoking or pulmonary disease; there was no retention in the liver, and only 1% of the activity that deposited in the lungs was detected in the urine after 24 hours. The authors concluded that most of the inhaled ultrafine particles were retained in the lung periphery and the conducting airways, without substantial systemic translocation or accumulation in the liver.

The other five papers focused on inhalation exposure to ultrafine carbon or ambient particles, four of these building on the associations between (cardio)vascular effects and pollution particles, and one examining the effects of particle inhalation on exercise performance. One study investigated the association between exposure to environmental nanoparticles, respiratory illness and mortality by comparing urban pollution levels (as particle numbers) and hospital admissions [3]. The results suggest that particle volume/mass from air pollution affects cardiovascular or respiratory disease admissions in the elderly, and particle numbers from traffic sources may affect admissions for paediatric asthma. [4] examined associations between pollution (particle mass) and coronary artery disease (CAD) in non-smoking elderly population. Significant positive associations were found between several pro-inflammatory markers (e.g. C-reactive protein, interleukin-6, soluble tumour necrosis factor receptor II and soluble P-selectin) and concentrations of quasi-ultrafine particulate matter (of $< / = 0.25 \ \mu m$ in diameter), fine elemental carbon, primary organic carbon, carbon black, total particle number, carbon monoxide and nitrogen dioxide. Inverse associations were found for some anti-oxidant markers. These results suggest that sources of primary organic carbon and quasi-ultrafine particles can lead to increased systemic inflammation and platelet activation, and decreased antioxidant enzyme activity in elderly people with CAD.

The effects of inhalation of ultrafine carbon particles (UFP) for 2 hours on systemic vascular or cardiopulmonary function during intermittent exercise have been studied [5, 6]. Although blood pressure, pre- or post-ischaemia forearm blood flow or resistance did not change, venous nitrate (but not nitrite) levels were significantly lower after exposure to UFP compared with air [5]. These results suggest that inhalation of UFP during intermittent exercise impairs peak forearm blood flow during reactive hyperaemia in healthy human subjects. A further volunteer study examined the effects on cardiopulmonary responses in healthy or asthmatic individuals of exposure to concentrated ultrafine particles (UFP) collected in an urban area with substantial motor vehicle pollution [6]. Exposures also lasted 2 hours with intermittent exercise. Relative to control (filtered air), UFP exposures were associated with a 0.5% mean

fall in arterial O_2 saturation and a 2% mean fall in forced expired volume in 1 sec the morning after exposure. However healthy and asthmatic subjects were not significantly different across most endpoints. This study suggests that ambient UFP can give rise to some acute deleterious cardiopulmonary responses.

The effects of inhalation of combustion-derived PM1 particles (aerodynamic diameter 0.02-2 μm) on exercise performance has been examined [7]. Reductions in work accumulated were reported between repeated trials with high doses of PM1, suggesting that acute inhalation of high PM1 typical of many urban environments could impair exercise performance.

2.2 Animal *in vivo* studies

Sixty-four publications were identified that examined the effects of nanoparticles in laboratory animals, of which:

Twenty-five have studied carbon nanotubes or other engineered carbon nanostructures;

Fifteen have examined the effects of inhalation of other engineered nanoparticles, including carbon black (3), silver (2), TiO_2 (3) and iron oxide (3); five have studied the effects of inhalation of non-engineered ultrafine particles;

Seven have reported on exposure of animals to engineered nanoparticles by other routes (dermal: 2; oral: 5) and 12 have reported toxicokinetic studies on nanoparticles.

2.2.1 Studies of multi-walled carbon nanotubes (MWCNTs)

Thirteen papers had been published reporting that following administration of MWCNTs by inhalation-type routes, animals showed inflammation and granuloma formation. Much of the concern over the potential health effects of MWCNTs has arisen out of comparisons with asbestos. Toxicologists define hazardous fibres as less than 3 μm in diameter, longer than 20 μm and biopersistent. Inhalation of such fibres can lead to severe lung diseases, such as lung cancer, asbestosis and mesothelioma. To address the question directly of whether CNTs can behave like asbestos, the mouse mesothelium was used as a model of the chest mesothelial cavity by Poland and co-workers:

Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Poland et al (2008) [8]

50 μg of different types of MWCNTs were injected into the mouse peritoneal cavity [8]. The materials tested were:

- NTlong 1 and NTlong 2, containing 24% and 84% fibres longer than 15 mm, and 12% and 77% longer than 20 mm respectively;

- NTtang 1 and NTtang 2, consisting of tangled aggregates of CNTs;

- Long fibre amosite (LFA) and short fibre amosite (SFA) asbestos;

- Nanoscale carbon black (CB).

Only the long fibres (LFA, NTlong 1 and NTlong 2) induced significant inflammation after 24 hours and granuloma formation on the peritoneal side of the diaphragm after 7 days. Water soluble or metallic contaminants of these fibres did not induce such responses. Frustrated phagocytosis was observed in response to LFA, NTlong 1 or NTlong 2, but not the other materials. These results demonstrate that in this assay system, long MWCNTs can behave like asbestos, conforming to the fibre paradigm. The authors point out that many questions remain unanswered: the biopersistence of these CNTs and whether they can migrate through the lung to the mesothelium; whether the changes seen would lead with time to

development of mesothelioma or other types of cancer, and whether sufficient exposure will occur in the workplace to lead to such changes in humans. Furthermore, other health effects not detected by this assay system might occur in response to the CNTs that did not induce asbestos-like effects.

[9] have also injected MWCNTs into the peritoneal cavity of mice, but the mice were heterozygous for p53 and are reported to be sensitive to asbestos and to develop mesothelioma more rapidly than wild-type animals [9]. Three materials were used (3 mg per mouse): MWCNTs, UICC crocidolite asbestos and C60 fullerenes. The MWCNT samples contained aggregates by light microscopy. After 10 days, the mice treated with MWCNTs had black spots of CNT aggregates and lesions on the peritoneal surface. The experiment was stopped after 25 weeks when 100% mortality was reached, first in the MWCNT group of mice followed by the crocidolite group. The lungs of the animals treated with MWCNTs had fibrous scars, foreign body granulomas and mesothelial lesions ranging from nodular mesotheliomas to large invasive tumours. The overall incidence of mesothelioma was 87.5% in the MWCNT group and 77.8% in the crocidolite group; no tumours were seen in the control or fullerene-treated animals. The authors suggest that these results demonstrate that MWCNTs induce mesothelioma when injected intraperitoneally, although they point out that further studies are required to investigate the persistence of the material and the effects of the iron it contains.

Two letters were published in response to the paper of Takagi et al, voicing several criticisms of the work [10, 11]. The major flaws identified by these correspondents were the large dose, poor characterisation of the materials and the fact that the p53 heterozygous mouse model has not been validated for this type of work. Donaldson et al detected inflammation in their model at a dose as low as 0.1 mg or 30,000 times lower than Takagi et al used; the large dose may have contributed to the agglomeration of the CNTs, leading to artefactual responses. The large dose and potential for over-reporting by this mouse model may have led to exaggerated responses that both sets of correspondents suggest may not be helpful for assessing the risks of human exposure to CNTs. In their responses, Takagi et al note that they have initiated studies with lower doses of CNTs, and observed mesothelioma in response to doses as low as 3 mg per animal.

Chiaretti et al have reported that after intraperitoneal administration of MWCNTs, there was no antigenic reaction, no inflammatory reaction nor modification of immunoglobulins, suggesting no modification of humoral immunity [12]. (These authors also showed that MWCNTs inhibited the proliferation of several cell types *in vitro*: the epithelial cell line MCF-7 and smooth muscle cells, but not the gut cell line Caco-2).

The toxicological effects of MWCNTs have been ascribed to different physical and chemical properties, including length, hydrophilicity or the presence of metal catalysts. Fubini and coworkers have performed systematic studies to explore this:

Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: physicochemical aspects. Fenoglio et al (2008) [13].

Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: toxicological aspects. Muller et al (2008) [14].

MWCNTs were modified by (i) grinding (introducing structural defects) and subsequently heating either in a vacuum to 600°C (to reduce oxygenated carbon functionalities and metallic oxides) or in an inert atmosphere at 2400°C to eliminate metals and repair the structural defects, or (ii) by heating at 2400°C in an inert atmosphere and subsequently grinding the thermally treated CNT (introducing defects in a metal-deprived carbon framework) [13]. The original ground CNTs could scavenge hydroxyl radicals; this property was lost by heating but restored upon grinding, suggesting that the radical-scavenging activity arises from structural defects in the CNTs. To investigate the *in vivo* consequences of these changes, the different MWCNTs were administered intratracheally to rats to

evaluate short-term and longer-term responses (3 & 60 days). The acute pulmonary toxicity and the genotoxicity of the CNTs were reduced upon heating but restored upon grinding, indicating that the toxicity of CNT may also be mediated by the presence of defective sites in their carbon framework [14].

Discrepancies have been reported between studies investigating the effects of inhalation of CNTs, some researchers reporting pulmonary fibrosis, granuloma formation and/or inflammation, others not observing such phenomena. For example, Liu and colleagues observed multiple lesions following intratracheal instillation of MWCNTs in rats, which occurred in a dose- and time-dependent manner, suggesting a foreign tissue body reaction [15].   However, granulomas may arise due to the instillation of unbreathable CNT agglomerates [16].   This group instilled 1-100 µg of MWCNT (dispersed with albumin, containing more than 80% of agglomerates of breathable size), and after 1, 7, 30, 90, and 180 days, inflammation, apoptosis, fibrosis, respiratory parameters and granuloma formation were assessed. Histopathology found evidence only of apoptosis of alveolar macrophages.

The pulmonary lesions induced in rats given MWCNTs via intratracheal administration can be characterised by X-ray phase contrast imaging [17].   However, detection of CNTs themselves in biological tissues is challenging, and [18] have proposed a method based on detection via the nickel remaining in the MWCNTs. Using this approach, they reported that the after intratracheal instillation in rats, the MWCNTs do not cross the pulmonary barrier, and persist in lungs for 6 months.

[19] have investigated the effects of CNTs (MW and SW) on the lung and systemic inflammation induced by inhalation of LPS. 24 hours after treatment, both CNTs alone induced lung inflammation with increased pulmonary permeability, hyperfibrinogenemia and enhanced levels of pro-inflammatory cytokines, but they did not synergistically exacerbate lung inflammation elicited by LPS.

Another type of co-exposure has been investigated by [20]. Mice were given MWCNTs by pharyngeal aspiration and 12 hours later, they were exposed to ozone for 24 hours. In response to the CNTs, there were significant increases in polymorphonuclear leukocytes, protein, lactate dehydrogenase (LDH), tumor necrosis factor (TNF)-α, interleukin (IL)-1β and mucin levels in bronchoalveolar lavage (BAL) fluid after 5 and 24 hours, but there were no additive or synergistic effects of subsequent exposure to ozone. The authors suggest this lack of effect may be due to the development of "cross-tolerance" reported for some sequentially administered pollutants.

2.2.2 Studies of single-walled carbon nanotubes (SWCNTs)

Nine publications were identified that considered the effects of SWCNTs when administered to laboratory animals. Two papers by Shvedova and coworkers have investigated the effects of inhalation exposure to SWCNTs in mice, the first comparing the commonly used administration method of pharyngeal aspiration with inhalation, their results having important implications for interpretation of data generated by routes other than inhalation:

Inhalation vs. aspiration of single-walled carbon nanotubes in C57BL/6 mice: inflammation, fibrosis, oxidative stress, and mutagenesis. Shvedova et al (2008) [21]

Pharyngeal aspiration of purified SWCNTs by mice has previously been shown to cause dose-dependent granulomatous pneumonia, oxidative stress, acute inflammation and fibrosis. In this study, inhalation of stable and uniform SWCNT dispersions (iron content of 17.7% by weight) at 5 mg/m^3, 5 h/day for 4 days was compared with pharyngeal aspiration of varying doses (5–20 µg per mouse) of the same material. Inhalation was more effective than aspiration in causing inflammatory responses, oxidative stress, collagen deposition and fibrosis.

Resolution of pulmonary inflammation requires timely apoptosis of neutrophils and their clearance by macrophages. The second paper by Shvedova and co-workers considers the role of NADPH oxidase in this process [22]. They found that mice lacking NADPH oxidase responded to SWCNT with a marked accumulation of neutrophils, elevated levels of apoptotic cells in the lungs, production of pro-inflammatory cytokines, decreased production of the anti-inflammatory and pro-fibrotic cytokines and reduced collagen deposition, compared to control mice. These results suggest that NADPH oxidase-derived reactive oxygen species may regulate the transition from the acute inflammation to the chronic fibrotic stage through apoptosis of neutrophils.

Another paper has further dissected the mechanisms that may underlie some of these inhalation responses to SWCNTs:

Single-walled carbon nanotubes can induce pulmonary injury in mouse model. Chou et al (2008) [23]

Intratracheal instillation of 0.5 mg of SWCNT into mice induced alveolar macrophage activation, chronic inflammatory responses and severe pulmonary granuloma formation. The authors analysed the gene expression changes in macrophages that accompany these responses using Affymetrix microarrays and a biological pathway analysis. They found that transcription factors such as NF-κB and AP-1 are activated, leading to oxidative stress, the release of pro-inflammatory cytokines, recruitment of leukocytes and activation of T cells. The authors propose that the innate and adaptive immune responses may contribute to the chronic pulmonary inflammation and granuloma formation observed *in vivo* in response to SWCNT.

For delivery of SWCNTs *in vivo*, an acoustic feeder system was designed to produce a respirable aerosol of 5 mg/m^3. The starting material was as-produced powder by the HiPCO method. The feed rate could be adjusted up to 25 mg/m^3. The powder particles were reduced in size using a mill that produced high shear forces, tearing the agglomerates apart. The resulting aerosol was size-separated using a settling chamber and two cyclones to produce a respirable aerosol [24].

Four publications have reported the application of Raman spectroscopy for detection of CNTs *in vivo* and in *ex vivo* tissues. [25] followed the distribution of SWCNTs in mice after intravenous administration over 3 months. They detected SWCNTs in the intestine, faeces, kidney and bladder, suggesting excretion and clearance of SWCNTs via the biliary and renal pathways. No toxic side effects were observed. [26] carried out similar studies, following long-term accumulation and toxicity of intravenously injected SWCNTs in organs such as liver, lung and spleen in mice over 3 months by Raman spectroscopy and transmission electron microscopy. In the third study, mice were monitored for 4 months after intravenous injection of SWCNTs; there was no evidence of toxicity and only age-related changes were noted at necropsy [27]. Histology and Raman microscopy showed that the SWCNTs persisted in macrophages of the liver and spleen for 4 months. [28] have followed targeting of SWCNTs to tumours in mice using Raman spectroscopy. Collectively these studies demonstrate both the usefulness of Raman spectroscopy for following distribution and the low toxicity of SWCNTs following intravenous administration.

When implanted into rat muscle, SWCNTs were phagocytosed by macrophages and transported to local lymph nodes whilst MWCNTs formed large aggregates within the tissue [29].

Three publications have studied the effects *in vivo* of other types of engineered, carbon-derived nanomaterials. The toxicity single-walled carbon nanohorns (SWNHs), a tubular nanocarbon containing no metal impurities, has been tested *in vivo* and *vitro* [30]. The SWNHs were not irritating or sensitizing, and they were negative in mutagenic and clastogenic tests. The lethal dosage for rats was more than 2,000 mg/kg of body weight.

Following intratracheal instillation, little damage to rat lung tissue was observed, although there was black pigmentation due to accumulation of the nanohorns. These results suggest that as-grown SWNHs have low acute toxicity.

The effects of repeated nose-only administration (3h per day for 10 days) of C-60 fullerene nano- or microparticles (55 nm or 930 nm in diameter respectively) have been studied in rats [31].   Both types of material induced minimal toxicological changes, with no gross or microscopic lesions, although the lung particle burdens were greater in nanoparticle-exposed rats than in microparticle-exposed rats. The lung half-lives for the nano- and micro-particles were 26 and 29 days, respectively.

[32] report the results of pulmonary administration of a novel class of self-assembling rosette nanotubes, which are water-soluble and free of metals. An acute inflammatory response was triggered with 25 and 50 μg after 24 hours (not with lower doses).   The lung inflammation resolved by 7 days. The authors suggest that these novel nanostructures may not suffer from the same toxicity concerns of other CNTs.

2.2.3 Studies of inhalation of other engineered nanomaterials

Three papers have investigated the effects of inhalation of carbon black (CB). To explore the cardiovascular effects of inhalation of CB, rats were whole-body exposed to a high dose of CB or filtered air for 6 hours/day, 5 days a week for 4 weeks [33]. CB was detected in pulmonary macrophages, but not in other tissues including liver, spleen and aorta. The CB exposure raised blood pressure, and levels of circulating inflammatory marker proteins, including monocyte chemoattractant protein-1, interleukin-6, and C-reactive protein.

The effects of CB on antigen-presenting cells in the lung were evaluated in mice, by intratracheal administration of 14 or 57 nm CB in the presence or absence of ovalbumin [34]. It was reported that exposure to the 14 nm CB increased the expression of MHC class II, co-stimulatory molecules and the number of antigen-presenting cells in the lung, especially in the presence of antigen, which can result in antigen-related airway inflammation.

The nasal toxicity of CB was studied in a sub-chronic exposure study in rats [35]. Animals were exposed to 0, 1, 7 or 50 mg/m³ of high surface area CB (HS-CB; primary particle size 17 nm; particle surface area 300 m²/g) or 50 mg/m³ of low surface area CB (LS-CB; primary particle size 70 nm; particle surface area 37 m²/g) for 6 hours/day, 5 days/week for 13 weeks. Rats were sacrificed after 1 day, 13 weeks or 11 months. Animals exposed to the middle or high doses of HS-CB had nasal inflammation and epithelial lesions after 1 day, which had mostly resolved by 13 weeks. Low-dose HS-CB or high-dose LS-CB induced only minimal epithelial lesions. The severity and persistence of CB-induced nasal toxicity in rats therefore depend on dose and particle surface area.

Two publications considered the effects of inhalation of silver nanoparticles.   The first reported a 90-day inhalation study in rats:

Lung function changes in Sprague-Dawley rats after prolonged inhalation exposure to silver nanoparticles. Sung et al (2008) [36]

Rats were exposed to low, medium or high doses of silver nanoparticles (0.7, 1.4 or $2.9.10^6$ particles/cm³; 18 nm diameter) for 6 hours/day in an inhalation chamber for 90 days. There were significant reductions in lung function (tidal volume and minute volume) after 90 days, and significant inflammation (only in the high-dose females). Histopathological examinations indicated dose-dependent increases in lung lesions, such as chronic alveolar inflammation, including thickened alveolar walls and small granulomatous lesions. These results suggest that inhalation of nano-scale silver particles can induce lung function changes and chronic inflammation following prolonged exposures.

The second publication examined the effects of repeated inhalation of silver nanoparticles on the nasal respiratory mucosa [37]. The animals were exposed to low, medium or high doses of silver (1.7, 12.7 or 132.10^4 particles/cm^3) in an inhalation chamber for 6 hours/day, 5 times/week for 28 days. There were no histopathological changes in the nasal cavity or lungs of exposed animals, but there was a slight increase in neutral (but not acid) mucins, and in the size and number of goblet cells.

Two publications report the effects of inhalation of titanium dioxide (TiO_2) in rats. The first study reported acute effects in rats:

The acute proinflammatory and prothrombotic effects of pulmonary exposure to rutile TiO2 nanorods in rats. Nemmar et al (2008) [38].

The acute effects (after 24 hours) of intratracheal instillation of rutile TiO_2 nanorods (1 and 5 mg/kg b.w.) in rats were investigated. The nanorods caused lung and systemic inflammation, with increased numbers of macrophages and neutrophils in bronchoalveolar lavage (BAL) fluid, increases in the numbers of monocytes and granulocytes in the blood, pulmonary and cardiac oedema. There were reduced numbers of platelets in response to exposure to 5 mg/kg and addition of the nanorods to rat blood *ex vivo* dose-dependently induced platelet aggregation.

A significantly larger dose of TiO_2 (50 mg/kg b.w.) was administered to female rats by intranasal instillation with analysis after 30 days [39]. Two types of TiO_2 were compared: 80 nm rutile and 155 nm anatase. Pathological changes were noted in the kidney, but not in the liver, spleen or heart. TiO_2 was however detected in the brain. These results suggest that TiO_2 enters the systemic circulation and is excreted by the kidneys, and may enter the brain either via the blood-brain barrier or the olfactory route.

A third publication examined the allergic reactions induced by TiO_2 and carbon black in grass pollen-sensitised rats [40]; no abstract is available and therefore further details can not be provided.

Three papers have examined the effects of inhalation of iron oxide nanoparticles in rodents. Iron oxide particles with mean diameters of 22 and 280 nm were intratracheally instilled into rats at low (0.8 mg/kg b.w.) or high (20 mg/kg b.w.) doses [41]. Lung inflammation occurred with increases in the numbers of inflammatory and immune cells, and pathological changes including follicular hyperplasia, protein effusion, pulmonary capillary vessel hyperaemia and alveolar lipoproteinosis. In response to the higher dose, overloading of the alveolar macrophages was noted, particles that had not been phagocytosed entering the lung epithelium. After 30 days, blood coagulation parameters were altered (lengthened prothrombin and activated partial thromboplastin times). Another paper reported that intranasal instillation of iron oxide nano- or submicron-sized particles led to transition metal imbalances in the brain, with greater accumulation of iron oxide in the brain from instillation of nano-sized than larger particles [42]. Superparamagnetic iron oxide nanoparticles can be detected in the lung after nose-only administration by magnetic resonance imaging [43].

A further two papers have examined the effects of inhalation of SiO_2 particles in rats. Wang and coworkers reported that inhalation of SiO_2 nanoparticles (100 or 300 mg/m^3) for 2 hours elevated several inflammatory markers in the lung (total numbers of cells, LDH, alkaline phosphatase and protein in the BAL fluid) and hydroxyproline in lung tissue more than micron-sized particles [44]. The second publication reported oxidative effects of inhalation of SiO_2 nanoparticles in rats, but no abstract is available and therefore further details can not be provided [45].

Understanding the distribution of nanoparticles after inhalation is important for investigating their potential toxicity. Kwon and colleagues have studied the distribution of fluorescent magnetic nanoparticles (50 nm) in mice following inhalation in a nose-only exposure chamber system with a low or high concentration of particles ($4.9.10^5$ and $9.3.10^5$/cm^3) for 4

hours per day, 5 days per week for 4 weeks [46]. The distribution was studied by MRI and confocal laser scanning microscopy. The particles were found in many organs, including the liver, testis, spleen, lung and brain.

The final publication in the category of inhalation of engineered nanomaterials considered the effects of exposure of rats to "Magic Nano" products. In 2006, there was a series of cases of pulmonary illness arising from use of the aerosol-can sprays "Magic Nano Glass & Ceramic" and "Magic Nano Bath". It was established that these products did not contain stable / solid nanoparticles, but the use of the "nano" name had implications for risk communication in the nanotechnology arena. To compare the toxicity of these two products with the "Magic Nano" pump spray, which had not caused the same health problems, rats were exposed by nose-only inhalation for 2 or 4 hours to these products [47]. "Magic Nano Glass & Ceramic" caused mortality at and above doses of 2,269 mg/m^3, with a time-adjusted 4 hour LC_{50} of 5,098 mg/m^3, whilst the "Magic Nano" pump spray was lethal at and above 81,222 mg/m^3 and the "Magic Nano Bath" did not cause mortality up to 21,100 mg/m^3. The affected animals showed upper and lower respiratory tract irritation, lung inflammation (changes in BAL fluid), oedema, haemorrhage and focal septal thickening. The volatile substances in the products rather than particle size appeared to be the key determinant of the toxicity.

Four publications were identified that considered the effects of inhalation of ultrafine (not engineered) nanoparticles, which are of lower priority for this bulletin [48-50]. One paper is of interest however since it may be useful for consideration of responses of sensitive individuals to nanoparticles in the workplace: the effects of allergen sensitization on deposition of ultrafine particles in the lungs were investigated. Ovalbumin-sensitized and non-sensitized mice were exposed by inhalation for 1 h to ultrafine, radiolabelled iridium particles [51]. The sensitized mice showed a relative increase in ultrafine deposition compared to non-sensitized mice, but only when the inhalation occurred before allergen challenge. This suggests that allergen sensitization can affect ultrafine deposition in the airways, but the relationship to effects in allergic individuals remains to be elucidated.

2.2.4 Studies of dermal exposure to engineered nanomaterials *in vivo*

Two studies were identified that have investigated dermal penetration of nanoparticles in rodents. The aim of the first study was to examine the effects of exposure to ultra-violet light (UV) on absorption of nanoparticles, a topic of relevance for consideration of the effects of sun exposure of skin treated with sunscreens containing nanomaterials [52]. Quantum dots (QD) were used as model nanoparticles. They were applied to the skin of mice in a glycerol vehicle with and without UV exposure. After 8 and 24 hours, penetration of the QD into the skin (assessed by tissue histology, confocal microscopy, and transmission electron microscopy (TEM) with EDAX analysis) was low in both the UV and non-UV exposed mice, although qualitatively higher levels of penetration were observed in the UV exposed mice.

The second publication, a meeting abstract, reported absorption of nanoparticles through mouse skin, but no abstract is available and therefore further details can not be provided [53].

2.2.5 Studies of oral exposure to engineered nanomaterials *in vivo*

The oral toxicity of silver nanoparticles has been investigated in a guideline-compliant 28-day study:

Twenty-eight-day oral toxicity, genotoxicity and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats. Kim et al (2008) [54]

The study was conducted according to the OECD guideline method 407 and GLP.

Four groups of rats (10 per group) were given vehicle, low dose (30 mg/kg b.w.), medium dose (300 mg/kg b.w.) or a high dose (1000 mg/kg b.w.) of silver nanoparticles (60 nm) by the oral route. After 28 days, there was no change in body weight, but dose-dependent changes in serum alkaline phosphatase and cholesterol were noted that might indicate some liver damage in response to doses of 300 mg/kg b.w. or more. There was no evidence of genotoxicity. Silver was dose-dependently detected in all the tissues studied, most significantly in the kidneys, where there was a significant gender-difference, with a 2-fold increase in the female kidneys compared with the male kidneys.

Changes in the liver were also observed in mice fed silver nano- or micro-particles (13 nm or 2-3.5 μm respectively) [55]. In the livers of both groups of animals, lymphocyte infiltration was seen after 3 days and expression of genes related to inflammation and apoptosis were altered. On the basis of changes in DNA content of a human hepatoma cell line exposed to the particles *in vitro,* the authors propose that the silver nanoparticles induce more apoptosis and inflammation than the micron-sized particles.

Effects in the liver have also been noted after feeding mice micron or nano-sized silica particles [56]. After 10 weeks, animals fed nanoparticles showed increased levels of alanine aminotransferase in blood, and there was also some fatty liver pattern in the livers by histological staining, although the silica contents of the livers in the two groups of animals were the same.

The acute oral toxicity of 20 and 120 nm zinc oxide nanoparticles has also been evaluated in mice, at doses of 1, 2, 3, 4 or 5 g/kg b.w.. Zinc was mainly detected in the bone, kidney and pancreas in response to administration of both sizes of particle. Increases in blood viscosity were seen with both types of particle, but only the 120 nm ZnO induced dose-dependent pathological damages in the stomach, liver, heart and spleen. Negative dose-dependent damage was noted in the liver, spleen and pancreas in response to the 20 nm particles. The authors conclude that the liver, spleen, heart, pancreas and bone are the target organs for both sizes of ZnO following oral exposure [57].

Oral consumption of nanoscale calcium-enriched milk in ovariectomized rats for 18 weeks led to increased bone/alkaline phosphatase ratios and urinary excretion of calcium compared to control or animals fed calcium carbonate or ionized calcium-enriched milk [58].

2.2.6 Toxicokinetic studies of engineered nanomaterials *in vivo*

Six publications have examined the distribution of nanoparticles *in vivo* after injection. The distribution of titanium dioxide nanoparticles after single intravenous injection of 5 mg/kg into mice was analysed after 1, 14 and 28 days [59]. The animals were healthy with normal behaviour throughout the study. TiO_2 was not detected in blood, brain or plasma; the highest levels were seen in liver, then spleen, lung and kidney. TiO_2 was retained in the liver for 28 days; the levels decreased slightly over time in the spleen, and had returned to normal by day 28 in the lung and kidney. There were no obvious toxic effects, no inflammatory response and no changes in organ function. On the basis of these results, the authors suggest that TiO_2 nanoparticles could be used safely in low doses. Similar results were obtained by [60]. After intravenous injection of 15 nm (primary particle size) TiO_2 nanoparticles into mice, the titanium level significantly increased in blood and many tissues, except the brain. Most of the titanium was found in the liver but this decreased with time (~30% over 1 month). This paper also noted that many foods contain high levels of TiO_2.

A third study administered gold nanoparticles (15, 50, 100 or 200 nm) by intravenous injection into mice (1 g/kg b.w.) [61]. After 24 hours, accumulation of the gold nanoparticles occurred in the liver, lung, spleen, kidney, brain, heart, stomach and was size-dependent: the smallest particles showed the most widespread distribution, with the 15 and 50 nm

nanoparticles crossing the blood-brain barrier. A further study followed the distribution of QD for 6 months in mice after a single intravenous injection [62].   The QD persisted and accumulated in the spleen, liver, and kidneys for at least 28 days, with partial elimination by 6 months. Mitochondrial alterations were noted in renal epithelial cells after 28 days and 6 months. On the basis of the results, a physiologically based pharmacokinetic computer simulation model was developed with excellent predictive capability for the time-dependent kinetic and distributional changes of the QD.

The biochemical compositions of serum, urine, extracts of liver and kidney have been assessed by NMR after administration of copper nanoparticles at doses of 50, 100 or 200 mg/kg b.w. per day for 5 days (route of administration not specified in abstract) [63]. Dose-dependent hepatotoxicity and nephrotoxicity were seen, and it was suggested by the authors that an increase in triglycerides in the serum, liver and kidney tissues could serve as a sensitive biomarker reflecting the lipidosis induced by nano-copper.

After subcutaneous injection of silver nano- or micron-sized particles into rats (63 mg/kg b.w.), [64] reported that silver nanoparticles translocated into the brain (as particles) and the authors suggest that they could induce neurodegenerative effects if they accumulate over a prolonged period of time.

A further six publications reported *in vivo* effects of engineered and other nanoparticles in meeting abstracts; insufficient details were given for reporting in the bulletin [65-70].

2.3 *In vitro* studies

Many of the *in vitro* studies initially identified reported development and characterization of nanoparticles for clinical applications, which are not relevant for and not included in this bulletin. One study of note however employed a novel system (embryonic zebrafish) as a dynamic whole animal assay to investigate the importance of chemical composition, size, surface functionalisation and route of exposure on interactions between nanomaterials and biological systems [71].

Fifty-two publications were identified that have used *in vitro* systems to examine the toxicity of engineered nanoparticles (and 14 on ambient or incidentally generated nanoparticles).

2.3.1 Studies of respiratory exposure to engineered nanomaterials *in vitro*

Different *in vitro* models have been used to examine the respiratory toxicity of nanoparticles. [72] compared internalisation of nano- and micron-sized particles by human alveolar type (AT) I (immortalised) and II (primary) cells. They found that ATI cells internalise many more particles than ATII cells, and show a preference for negatively charged particles.

In the human Calu3 pulmonary epithelial cell line, rosette CNTs have no effects on cell viability, and induce changes in messenger RNA for IL-8 only in response to the highest doses suggesting that these CNTs have weak pro-inflammatory activity [73]. Another study using Calu-3 cells has shown that CNTs can interfere with formation of the respiratory barrier if added to the cultures as the trans-epithelial resistance develops without affecting cell viability [74]. This effect was more pronounced in response to MWCNTs than SWCNTs or carbon black.

The uptake and effects of CNT-derived nanoloops and gold nanoparticles have been studied in polarised lung and colon epithelial cells [75]. Both types of material were taken up by the cells, aggregated and transported to the basal cellular surface. Other effects were cell- and particle-type dependent: e.g. citrate-capped gold particles passed into lung and gut cells through small pores in the cell membranes, potentially generated by lipid peroxidation.

The effects of metal nanoparticles have been investigated in several *in vitro* studies. Two reports compared the toxicity of metal nanoparticles and CNTs in A549 respiratory cells [76, 77]. MWCNTs were more toxic than aluminium oxide or titanium oxide nanoparticles, whilst copper nanoparticles were more toxic than other metal oxides or MWCNTs in terms of cytotoxicity and DNA damage, an effect that was not due to generation of copper ions.

Zinc oxide nanoparticles induced oxidative stress and disturbed calcium homeostasis in human bronchial epithelial cells (BEAS-B) [78]. In both BEAS-2B and macrophage (RAW 264.7) cells, ZnO nanoparticles induced toxicity, with generation of reactive oxygen species (ROS), oxidant injury, inflammation and cell death. Undissolved ZnO nanoparticles entered caveolae and lysosomes in BEAS-2B and RAW 264.7 cells respectively, whilst fluorescently labelled CeO_2 nanoparticles were taken up into endosomes in both cell types, without inducing inflammation or cytotoxicity [79]. Instead, CeO_2 suppressed ROS production and induced cellular resistance to an exogenous source of oxidative stress. Fluorescently labelled TiO_2 were processed by the same uptake pathways as CeO_2 but did not elicit any adverse or protective effects. In other human bronchial epithelial cell lines (Chago-K1) however, TiO_2 nanoparticles induced cytotoxicity, even when the cells were exposed to the nanoparticles in the dark [80]. These results demonstrate that metal oxide nanoparticles induce a range of biological responses that vary from cytotoxic to cytoprotective.

Moss and colleagues has hypothesised that macrophage responses to nanoparticles may reflect the cumulative projected area of the particles i.e. the degree to which the surface of the macrophage becomes shielded from other objects or molecules, thereby reducing its

ability to clear other particles [81]. *In vitro*, the observed decrease in macrophage-mediated alveolar clearance of polystyrene test particles can be directly related to the potential for TiO_2 particles to mask the surface of the macrophage such that both nanoparticle number and surface area are relevant to their ability to affect macrophage function and clearance of particles.

A number of papers have investigated the potential genotoxicity of engineered and ambient nanoparticles in respiratory and other cell types; e.g. [82, 83]. In the FE1-Muta™ mouse lung epithelial cell line, SWCNTs and C60 fullerenes are less genotoxic than carbon black or diesel exhaust particles [84].

There has been much debate about appropriate *in vitro* models for testing the respiratory toxicity of nanoparticles [85]. Holden and co-workers have compared air-liquid interface (ALI) with suspension delivery of nanoparticles (diesel exhaust) on human bronchial epithelial cells, and found that although both methods reduce cell viability and induce expression of IL-8, ALI delivery induces these effects at doses that are several orders of magnitude lower than suspension [86]. [87] have compared human and rat lung epithelial cell responses to TiO_2 with those observed *in vivo*, and found little correlation for the endpoints that they studied, including release of LDH, changes in MTT or total protein.

New models are being developed for studying the toxicity of nanoparticles in the airways; e.g. MucilAir developed by Epithelix is a new 3D human airway model [88]. [89] has estimated human exposure to SWCNTs in 3D tissue-engineered human lung.

2.3.2 Studies of dermal exposure to engineered nanomaterials *in vitro*

Two studies from the group of Monteiro-Riviere have investigated penetration of QDs across skin *in vitro*. In the first study, they found QDs in the stratum corneum and around hair follicles in isolated pig skin (after topical application of 1, 2 or 10 μM for 24 hours) [90]. In human epidermal keratinocytes (HEK), incubation with the QDs reduced cell viability and induced release of the cytokines IL-6 and IL-8. The group then investigated penetration of QDs in isolated pig skin during flexing or after abrasion, two scenarios of relevance for potential human dermal exposures to nanomaterials:

Assessment of quantum dot penetration into intact, tape-stripped, abraded and flexed rat skin. Zhang et al (2008) [91]

Dermal penetration of QD coated with carboxylic acid was studied in flow-through diffusion cells containing flexed, tape-stripped and abraded rat skin. Normal intact, tape-stripped and flexed skin did not show QD penetration after 8 or 24 h, although flexing increased the number of QD on the surface of skin. Tape-stripping detected QD only on the surface of the viable epidermis. However the QD penetrated into the viable dermal layers of abraded skin after both 8 and 24 h although they were not detected in the perfusate at any time point. These results suggest that QD do not penetrate beyond the uppermost stratum corneum layers of intact rat skin, but abrasion allows QD to penetrate deeper into the dermal layers.

In a further study by this group, they have shown that applying physiological load to HEK cells increases cell membrane permeability and uptake of nanoparticles, as well as increasing cytokine production and reducing cell viability [92].

A study by Sonovane and coworkers has also used isolated rat skin and gut to investigate penetration of gold nanoparticles:

In vitro permeation of gold nanoparticles through rat skin and rat intestine: Effect of particle size. Sonavane et al (2008) [93]

Permeation of gold nanoparticles (15, 102 or 198 nm) was analysed in isolated rat skin in Franz diffusion cells and in isolated rat gut in the 'intestinal sac' method, using UV–visible

spectroscopy, ICP mass spectrometry, TEM and energy dispersive X-ray spectroscopy (EDS).   Penetration in both model systems was size-dependent: 15 nm nanoparticles showed higher permeation than larger particles, the permeability coefficient and diffusion coefficient decreasing with increasing size.   Permeation was higher through intestine than skin. TEM analysis revealed accumulation of smaller nanoparticles in deeper regions of skin whereas the larger particles were observed mainly more superficial layers.

Gold nanorods have been shown to be more toxic to human skin cells than spherical gold nanoparticles, due to their CTAB coating [94].

2.3.3 Studies of effects of engineered nanomaterials in other cell types *in vitro*

Five other studies have examined the cytotoxicity of CNTs and fullerenes in human cells. [95] have reported that in human peripheral blood lymphocytes, SWCNTs decrease cell growth and metabolism, but no effects on cell death, apoptosis or DNA damage were observed. Two studies by Pacurari and coworkers have examined the effects of CNTs in normal and malignant human mesothelial cells. Both SWCNTs and MWCNTs caused cell death, cytotoxicity, DNA damage and apoptosis in these cells [96, 97].   In fibroblasts, [98] has shown that the rates of endocytosis and exocytosis of SWCNTs are closely matched. One study has considered the best suspension method to use for CNTs *in vitro* [99].

[100] compared the effects of titanium dioxide and other metallic oxide nanoparticles on human astrocytic cells (U87) and normal human fibroblasts. Both micro- and nano-particles induced cell death in both human cell types in a concentration-related manner: ZnO nanoparticles were more potent than the TiO_2, which were more potent than the MgO. In mouse L929 fibroblast cells, TiO_2 dose-dependently induced apoptosis, increases in the numbers of lysosomes, oxidative stress and LDH release [101].   HeLa and Jurkat cells take up fluorescent poly-isoprene nanoparticles very readily into endosomes, to a much greater extent than other polymeric nanoparticles [102].

In a cell line model (U937) of leukocytes, [103] reported that doses of nanoparticles of cobalt but not TiO_2 that do not cause cytotoxicity, resulted in generation of reactive oxygen species, up-regulation of mRNA for matrix metalloproteinases (MMP-2 and 9) and increased gelatinolytic activities, as well as dose- and time-related decreases in tissue inhibitors of metalloproteinases (TIMP-2).   Thus the balance of MMPs to TIMPs is disrupted by the nanoparticles.

[104] used a triple cell co-culture system of epithelial cells, macrophages and dendritic cells (DC) to test the toxicity of titanium dioxide; the nanoparticles were detected both as single particles not enclosed in membranes in the cells and as membrane-bound agglomerates. They increased generation of reactive oxygen species but not tumour necrosis factor α. Mature DC can take up magnetic nanoparticles (10-200 nm) into lysosomes [105], and carbon black nanoparticles (14 or 56 nm) have been shown to promote bone marrow derived DC maturation [106].

The human gut epithelial cell line Caco-2 has been used to study the effects of oral uptake of nanoparticles (e.g. [107]).   The cytotoxicity of QDs in this model is modulated by surface coating; e.g. acid treatment, mimicking low gastric pH, increases the toxicity, most likely due to damage or removal of the surface coating. [108] has compared uptake of nanoparticles into Caco-2, RAW macrophages and MDCK kidney cells, reporting that uptake was greatest in the macrophages and lowest in the Caco-2 cells. [109] used mouse epithelial (JB6) cells to examine the carcinogenic effects of alumina nanoparticles and reported increased proliferation, accompanied by increased reactive stress.

Although animal experiments reporting effects in reproductive systems are lacking, perfused human placenta has been used to show that PEG-ylated gold nanoparticles (10-30 nm) do not cross from the maternal into foetal circulation after 6h, although they are taken up by

BeWo choriocarcinoma cells *in vitro* [110]. Mouse Leydig TM3 cells, the testosterone-producing cells of the testis, can take up diesel exhaust, TiO_2 and CB nanoparticles, leading to effects on cell viability, proliferation and gene expression. The outcomes were unique for each nanoparticle, such that TiO_2 was the most cytotoxic; TiO_2 and diesel exhaust inhibited proliferation, and CB and diesel exhaust modified gene expression [111].

2.3.4 Studies of effects of engineered nanomaterials in acellular systems *in vitro*

Twelve reports were identified that have investigated the effects of nanoparticles on isolated, acellular biological systems. CNTs can increase the membrane porosity for several molecules (e.g. caffeine) of lipid bilayers [112]. Modification of MWCNTs can significantly modulate their effects on complement activation and binding of plasma proteins [113]. Using renal cell sediment, [114] reported that gold nanoparticles can penetrate into renal cells.

A number of reports have suggested that nanoparticles can induce neurodegeneration and kill neurones *in vitro*; [115] have now shown that ferritin nanoparticles decrease uptake of the neurotransmitter glutamate into isolated synaptosomes and dose-dependently increase levels of reactive oxygen species. Other effects have also been reported in neuronal systems: nanoparticles can promote fibrillation of β-amyloid [116] and affect microtubules, causing changes in the conformation of tubulin and its polymerisation; these effects could modulate many cellular functions in neuronal and other cells [117]. SWCNTs can inhibit endocytosis in neuronal cells, leading to an increase in neurite length [118]. [119] demonstrated dose- and time-dependent, receptor-mediated transport of conjugated quantum rods across a blood-brain barrier *in vitro*.

Several papers have reported techniques for assessing interactions of nanoparticles with cells; e.g. using zeta potential [120] or non-interferometric widefield optical profilometry [121]. [122] have developed a "ferric reducing ability of serum (FRAS)" assay as a screening tool to quantify the oxidative damage induced by nanoparticles in human blood serum. Antioxidants in blood protect against oxidative damage caused by free radicals via chemical quenching; several nanoparticles decreased the antioxidant capacity of serum (nano-silver, nano-carbon blacks, fullerene soot, and nano-TiO_2 (anatase), but not nano-alumina, fullerite, purified fullerene, fine TiO_2 (rutile) or Min-U-Sil 5). Particle surface area and not particle size were associated with level of oxidative stress.

2.3.5 Studies of effects of ambient nanoparticles *in vitro*

Ambient or incidentally generated nanoparticles have also been tested for toxicity *in vitro*. Nanoparticles released from therapeutic titanium implants can induce both apoptosis and necrosis in human U937 cells [123]. [124] has tested a range of environmental nanoparticles in A549 respiratory cells; cytokine release (IL-6, IL-8) was detected in response to silver, Fe_2O_3, asbestos and MWCNTs. Reactive oxygen species (ROS) production was also detected in response to silver, Fe_2O_3, ZrO_2, asbestos and MWCNT aggregates, as well as natural gas kitchen burner combustion nanoparticles.

Cellular oxidative stress after exposure to diesel exhaust particles has been investigated using time-of-flight secondary ion mass spectrometry (TOF-SIMS), reverse transcription polymerase chain reaction (RT-PCR) and scanning transmission electron microscopy (STEM) [125].

Eleven publications were identified of relevance for this section of the bulletin, but they were not available as abstracts for consideration: [126-136], covering a range of topics including effects of size and surface reactivity on toxicity.

2.4 Computational modelling

Two publications have developed models for examining workplace exposures to nanoparticles. A model-based approach has been proposed to assess the inhalation risk for workers in TiO_2 production factories [137]. A Hill model was used to reconstruct dose-response function based on data from rats exposed by chronic inhalation to poorly soluble fine and nano-sized particles. A physiologically based lung model was used to predict surface area-based TiO_2 burdens in the alveolar surface and interstitial granuloma. The exposure effect was characterized in the lung by increases in neutrophils and tumour proportion on the interstitium. The results suggest that processes are unlikely to pose substantial lung cancer risks.

In the second paper, [138] propose and illustrate the use of risk analysis Monte Carlo (MC) models to assess the cost and exposure trade-offs of the high-pressure carbon monoxide (HiPCO) SWCNT manufacturing process. The authors make assumptions regarding the timing, frequency, magnitude and expense of health and safety standards, modelling them as stochastic events and examining their impact on production costs and occupational exposure. They propose that these models could help policy makers and manufacturers explore potential health and safety benefits, and consequences.

Several publications have reported development of models for studying the interactions between nanoparticles and the body; two have contributed to the ongoing evolution of models of deposition of particles in the airways. [139] investigated the impact of inclusion of a larynx on a model of upper tracheobronchial airways to assess the flow and deposition of nanoparticles; it increased tracheal deposition of nano- and micron-sized particles and decreased bronchial deposition. [140] have reduced the complexity of a model of upper tracheobronchial airways into adjustable, triple bifurcation units, and compared results using the model with those from experiments and analytical modelling.

A stochastic approach has been developed for predicting the adhesion strength of nanoparticles to a cell layer under flow, such as occurring in blood vessels, coupled to a mathematical model for the receptor-mediated endocytosis of the nanoparticles [141]. Three different states for the particle/cell system have been predicted, namely no adhesion, adhesion with no endocytosis and adhesion with endocytosis, based upon the geometrical and biophysical properties of the particles and the biological conditions at the site of adhesion. Although formulated for design of therapeutic nanoparticles, these techniques could also provide information on adhesion of other absorbed nanoparticles within the vasculature.

[142] have used computer simulations to investigate the interactions between fullerenes and lipid membranes. They have shown that aggregates of fullerenes will disaggregate after entering the membrane from an aqueous suspension, but the small structural changes that they then induce in the bilayer are unlikely to induce cytotoxicity *per se.*

2.5 Reviews

The searches identified 45 articles reviewing the potential health effects of engineered nanomaterials.

Two reviews have focussed on how health surveillance might be carried out in workplaces where nanomaterials are handled. In the absence of an evidence base for nanomaterial-specific health surveillance, general medical screening for nanomaterials workers (that could form the foundation for future epidemiological studies) has been recommended with development of exposure registries [143]. Schulte and coworkers [144] reach similar conclusions. These authors have also written two other reviews, presenting a conceptual framework for risk management of nanomaterials' activities in the workplace [145], and the

critical questions that will help address knowledge gaps concerning the potential occupational hazards of these materials [146]. (An editorial was published considering the last of these reviews [147].

[148] reviews recent developments in nanotechnology including current manufacturing techniques, uses of nanoscale particles and their implications for particle toxicity and human exposure pathways, as well as current risk assessment methods. [149] and [150] discuss EHS needs and the progress being made by industry, academic institutions and government laboratories active in the nanomaterial field. Conti and co-workers report the findings of an international survey of nanomaterials companies and laboratories regarding their environmental health and safety (EHS) programs and associated risk beliefs [151]. Most of the nanospecific programs are based on general EHS programs but with recommendations for handling nanoparticles that include engineering controls, clothing, gloves, eye protection and respirators. Other surveys of the uses, potential numbers of workers exposed and safety measures have been conducted in Germany and Switzerland [152, 153].

Twenty-eight reviews were identified on the current state of knowledge of the toxicology and hazards that nanomaterials may present [154-158]. Some of these reviews have focused on workers [159-161]; others on consumers e.g. in the food industry [162] and other areas of nanotechnology [163]. Some authors have specifically reviewed how the risks of nanomaterials in food may be perceived [164] and a risk framework has been proposed for exposure assessment of nanomaterials in consumer products [165]. A number of other general reviews have been published on nanomaterials health and safety concerns, and how they might be addressed or regulated: [166-171] including in the agri-food sector [172].

The potential inhalation toxicity of nanoparticles has been reviewed by [173, 174] and the dermal toxicity by [175]. Some toxicological reviews focus on CNTs [176], fullerenes [177] and silver [178, 179]. Furthermore, several nanotoxicology papers were presented at the 236th National Meeting of the Division of Chemical Toxicology of the American Chemical Society [180-182]. The cosmetics company L'Oreal has reviewed its studies on the dermal effects of TiO_2 and ZnO, suggesting that particle chemistry not just size influence study outcome, and that overall, nano-sized cosmetic or sunscreen ingredients pose no potential risk to human health [183]. [184] has reviewed the potential mechanisms by which particulate pollutants, including ambient and engineered nanoparticles, exert their adverse effects through the generation of oxidative stress in the respiratory tract. Poma et al have reviewed the potential value in applying toxicogenomic approaches to aid understanding of nanotoxicology [185]. A critical appraisal tool has been reported and used to evaluate 28 studies of the health effects of nanoparticles [186].

2.6 Bibliography

1.   Zvyagin, A. V., Zhao, X., Gierden, A., Sanchez, W., Ross, J. A., and Roberts, M. S. (2008). Imaging of zinc oxide nanoparticle penetration in human skin in vitro and in vivo. *J Biomed Opt* **13,** 064031.
2.   Moller, W., Felten, K., Sommerer, K., Scheuch, G., Meyer, G., Meyer, P., Haussinger, K., and Kreyling, W. G. (2008). Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. *Am J Respir Crit Care Med* **177,** 426-32.
3.   Andersen, Z. J., Wahlin, P., Raaschou-Nielsen, O., Ketzel, M., Scheike, T., and Loft, S. (2008). Size distribution and total number concentration of ultrafine and accumulation mode particles and hospital admissions in children and the elderly in copenhagen, denmark. *Occup Environ Med* **65,** 458-66.
4.   Delfino, R. J., Staimer, N., Tjoa, T., Polidori, A., Arhami, M., Gillen, D. L., Kleinman, M. T., Vaziri, N. D., Longhurst, J., Zaldivar, F., and Sioutas, C. (2008). Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. *Environ Health Perspect* **116,** 898-906.
5.   Shah, A. P., Pietropaoli, A. P., Frasier, L. M., Speers, D. M., Chalupa, D. C., Delehanty, J. M., Huang, L.-S., Utell, M. J., and Frampton, M. W. (2008). Effect of inhaled carbon ultrafine particles on reactive hyperemia in healthy human subjects. *Environ Health Perspect* **116,** 375-80.
6.   Gong, H., Jr., Linn, W. S., Clark, K. W., Anderson, K. R., Sioutas, C., Alexis, N. E., Cascio, W. E., and Devlin, R. B. (2008). Exposures of healthy and asthmatic volunteers to concentrated ambient ultrafine particles in los angeles. *Inhal Toxicol* **20,** 533-45.
7.   Rundell, K. W., and Caviston, R. (2008). Ultrafine and fine particulate matter inhalation decreases exercise performance in healthy subjects. *J Strength Cond Res* **22,** 2-5.
8.   Poland, C. A., Duffin, R., Kinloch, I., Maynard, A., Wallace, W. A. H., Seaton, A., Stone, V., Brown, S., Macnee, W., and Donaldson, K. (2008). Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol* **3,** 423-8.
9.   Takagi, A., Hirose, A., Nishimura, T., Fukumori, N., Ogata, A., Ohashi, N., Kitajima, S., and Kanno, J. (2008). Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube. *Journal of Toxicological Sciences* **33,** 105-116.
10.   Donaldson, K., Stone, V., Seaton, A., Tran, L., Aitken, R., and Poland, C. (2008). Re: Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube. *J Toxicol Sci* **33,** 385; author reply 386-8.
11.   Ichihara, G., Castranova, V., Tanioka, A., and Miyazawa, K. (2008). Re: Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube. *J Toxicol Sci* **33,** 381-2; author reply 382-4.
12.   Chiaretti, M., Mazzanti, G., Bosco, S., Bellucci, S., Cucina, A., Le Foche, F., Carru, G. A., Mastrangelo, S., Di Sotto, A., Masciangelo, R., Chiaretti, A. M., Balasubramanian, C., De Bellis, G., Micciulla, F., Porta, N., Deriu, G., and Tiberia, A. (2008). Carbon nanotubes toxicology and effects on metabolism and immunological modification in vitro and in vivo. *Journal of Physics-Condensed Matter* **20**.
13.   Fenoglio, I., Greco, G., Tornatis, M., Muller, J., Rayrnundo-Pinero, E., Beguin, F., Fonseca, A., Nagy, J. B., Lison, D., and Fubini, B. (2008). Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: Physicochemical aspects. *Chemical Research in Toxicology* **21,** 1690-1697.
14.   Muller, J., Huaux, F., Fonseca, A., Nagy, J. B., Moreau, N., Delos, M., Raymundo-Pinero, E., Beguin, F., Kirsch-Volders, M., Fenoglio, I., Fubini, B., and Lison, D. (2008). Structural defects play a major role in the acute lung toxicity of multiwall carbon nanotubes: Toxicological aspects. *Chemical Research in Toxicology* **21,** 1698-1705.
15.   Liu, A. H., Sun, K. N., Yang, J. F., and Zhao, D. M. (2008). Toxicological effects of multi-wall carbon nanotubes in rats. *Journal of Nanoparticle Research* **10,** 1303-1307.
16.   Elgrabli, D., Abella-Gallart, S., Robidel, F., Rogerieux, F., Boczkowski, J., and Lacroix, G. (2008). Induction of apoptosis and absence of inflammation in rat lung after intratracheal instillation of multiwalled carbon nanotubes. *Toxicology* **253,** 131-136.

17.   Li, J. G., Xue, Y. L., Han, B., Li, Q. N., Liu, L. X., Xiao, T. Q., and Li, W. X. (2008). Application of x-ray phase contrast imaging technique in detection of pulmonary lesions induced by multi-walled carbon nanotubes in rats. *Journal of Nanoscience and Nanotechnology* **8,** 3357-3362.

18.   Elgrabli, D., Floriani, M., Abella-Gallart, S., Meunier, L., Gamez, C., Delalain, P., Rogerieux, F., Boczkowski, J., and Lacroix, G. (2008). Biodistribution and clearance of instilled carbon nanotubes in rat lung. *Particle and Fibre Toxicology* **5**.

19.   Inoue, K., Takano, H., Koike, E., Yanagisawa, R., Sakurai, M., Tasaka, S., Ishizaka, A., and Shimada, A. (2008). Effects of pulmonary exposure to carbon nanotubes on lung and systemic inflammation with coagulatory disturbance induced by lipopolysaccharide in mice. *Experimental Biology and Medicine* **233,** 1583-1590.

20.   Han, S. G., Andrews, R., Gairola, C. G., and Bhalla, D. K. (2008). Acute pulmonary effects of combined exposure to carbon nanotubes and ozone in mice. *Inhalation Toxicology* **20,** 391-398.

21.   Shvedova, A. A., Kisin, E., Murray, A. R., Johnson, V. J., Gorelik, O., Arepalli, S., Hubbs, A. F., Mercer, R. R., Keohavong, P., Sussman, N., Jin, J., Yin, J., Stone, S., Chen, B. T., Deye, G., Maynard, A., Castranova, V., Baron, P. A., and Kagan, V. E. (2008). Inhalation vs. Aspiration of single-walled carbon nanotubes in c57bl/6 mice: Inflammation, fibrosis, oxidative stress, and mutagenesis. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **295,** L552-L565.

22.   Shvedova, A. A., Kisin, E. R., Murray, A. R., Kommineni, C., Castranova, V., Fadeel, B., and Kagan, V. E. (2008). Increased accumulation of neutrophils and decreased fibrosis in the lung of nadph oxidase-deficient c57bl/6 mice exposed to carbon nanotubes. *Toxicology and Applied Pharmacology* **231,** 235-240.

23.   Chou, C. C., Hsiao, H. Y., Hong, Q. S., Chen, C. H., Peng, Y. W., Chen, H. W., and Yang, P. C. (2008). Single-walled carbon nanotubes can induce pulmonary injury in mouse model. *Nano Letters* **8,** 437-445.

24.   Baron, P. A., Deye, G. J., Chen, B. T., Schwegler-Berry, D. E., Shvedova, A. A., and Castranova, V. (2008). Aerosolization of single-walled carbon nanotubes for an inhalation study. *Inhal Toxicol* **20,** 751-60.

25.   Liu, Z., Davis, C., Cai, W. B., He, L., Chen, X. Y., and Dai, H. J. (2008). Circulation and long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by raman spectroscopy. *Proceedings of the National Academy of Sciences of the United States of America* **105,** 1410-1415.

26.   Yang, S. T., Wang, X., Jia, G., Gu, Y. Q., Wang, T. C., Nie, H. Y., Ge, C. C., Wang, H. F., and Liu, Y. F. (2008). Long-term accumulation and low toxicity of single-walled carbon nanotubes in intravenously exposed mice. *Toxicology Letters* **181,** 182-189.

27.   Schipper, M. L., Nakayama-Ratchford, N., Davis, C. R., Kam, N. W. S., Chu, P., Liu, Z., Sun, X. M., Dai, H. J., and Gambhir, S. S. (2008). A pilot toxicology study of single-walled carbon nanotubes in a small sample of mice. *Nature Nanotechnology* **3,** 216-221.

28.   Zavaleta, C., de la Zerda, A., Liu, Z., Keren, S., Cheng, Z., Schipper, M., Chen, X., Dai, H., and Gambhir, S. S. (2008). Noninvasive raman spectroscopy in living mice for evaluation of tumor targeting with carbon nanotubes. *Nano Letters* **8,** 2800-2805.

29.   Fraczek, A., Menaszek, E., Paluszkiewicz, C., and Blazewicz, M. (2008). Comparative in vivo biocompatibility study of single- and multi-wall carbon nanotubes. *Acta Biomater* **4,** 1593-602.

30.   Miyawaki, J., Yudasaka, M., Azami, T., Kubo, Y., and Iijima, S. (2008). Toxicity of single-walled carbon nanohorns. *Acs Nano* **2,** 213-226.

31.   Baker, G. L., Gupta, A., Clark, M. L., Valenzuela, B. R., Staska, L. M., Harbo, S. J., Pierce, J. T., and Dill, J. A. (2008). Inhalation toxicity and lung toxicokinetics of c-60 fullerene nanoparticles and microparticles. *Toxicological Sciences* **101,** 122-131.

32.   Journeay, W. S., Suri, S. S., Moralez, J. G., Fenniri, H., and Singh, B. (2008). Rosette nanotubes show low acute pulmonary toxicity in vivo. *International Journal of Nanomedicine* **3,** 373-383.

33.   Niwa, Y., Hiura, Y., Sawamura, H., and Iwai, N. (2008). Inhalation exposure to carbon black induces inflammatory response in rats. *Circ J* **72,** 144-9.

34.   Koike, E., Takano, H., Inoue, K. I., Yanagisawa, R., Sakurai, M., Aoyagi, H., Shinohara, R., and Kobayashi, T. (2008). Pulmonary exposure to carbon black nanoparticles increases the number of antigen-presenting cells in murine lung. *Int J Immunopathol Pharmacol* **21,** 35-42.

35.   Santhanam, P., Wagner, J. G., Elder, A., Gelein, R., Carter, J. M., Driscoll, K. E., Oberdorster, G., and Harkema, J. R. (2008). Effects of subchronic inhalation exposure to carbon black

nanoparticles in the nasal airways of laboratory rats. *International Journal of Nanotechnology* **5,** 30-54.

36.   Sung, J. H., Ji, J. H., Yoon, J. U., Kim, D. S., Song, M. Y., Jeong, J., Han, B. S., Han, J. H., Chung, Y. H., Kim, J., Kim, T. S., Chang, H. K., Lee, E. J., Lee, J. H., and Yu, I. J. (2008). Lung function changes in sprague-dawley rats after prolonged inhalation exposure to silver nanoparticles. *Inhalation Toxicology* **20,** 567-574.

37.   Hyun, J. S., Lee, B. S., Ryu, H. Y., Sung, J. H., Chung, K. H., and Yu, I. J. (2008). Effects of repeated silver nanoparticles exposure on the histological structure and mucins of nasal respiratory mucosa in rats. *Toxicology Letters* **182,** 24-28.

38.   Nemmar, A., Melghit, K., and Ali, B. H. (2008). The acute proinflammatory and prothrombotic effects of pulmonary exposure to rutile tio2 nanorods in rats. *Experimental Biology and Medicine* **233,** 610-619.

39.   Wang, J. X., Li, Y. F., Li, W., Chen, C. Y., Li, B., and Zhao, Y. L. (2008). Biological effect of intranasally instilled titanium dioxide nanoparticles on female mice. *Nano* **3,** 279-285.

40.   Rogerieux, F., Robidel, F., Abou-Chakra, O., and Lacroix, G. (2008). Effect of repeated intratracheal instillation of tio2 and carbon black nanoparticles on the allergic reaction in grass pollen-sensitised rats. *Allergy* **63,** 742.

41.   Zhu, M. T., Feng, W. Y., Wang, B., Wang, T. C., Gu, Y. Q., Wang, M., Wang, Y., Ouyang, H., Zhao, Y. L., and Chai, Z. F. (2008). Comparative study of pulmonary responses to nano- and submicron-sized ferric oxide in rats. *Toxicology* **247,** 102-111.

42.   Wang, B., Wang, Y., Feng, W. Y., Zhu, M. T., Wang, M., Ouyang, H., Wang, H. J., Li, M., Zhao, Y. L., and Chai, Z. F. (2008). Trace metal disturbance in mice brain after intranasal exposure of nano- and submicron-sized fe2o3 particles. *Chemia Analityczna* **53,** 927-942.

43.   Martin, A. R., Thompson, R. B., and Finlay, W. H. (2008). Mri measurement of regional lung deposition in mice exposed nose-only to nebulized superparamagnetic iron oxide nanoparticles. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* **21,** 335-341.

44.   Wang, J., Jin, Y.-h., Liu, B., Yu, Q.-l., Wang, K., and Zh, C.-x. (2008). Comparative study on the acute toxicity of pulmonary caused by nanosized and microsized powders of silicon dioxide. *Zhonghua Yufang Yixue Zazhi* **42,** 30-35.

45.   Jin, C., Jin, Y., Wang, J., and Zhao, C. (2008). [comparative study of the effect on oxidative damage in rats inhaled by nano-sized and micro-sized silicon dioxide]. *Wei Sheng Yan Jiu* **37,** 16-8, 36.

46.   Kwon, J. T., Hwang, S. K., Jin, H., Kim, D. S., Mina-Tehrani, A., Yoon, H. J., Chop, M., Yoon, T. J., Han, D. Y., Kang, Y. W., Yoon, B. I., Lee, J. K., and Cho, M. H. (2008). Body distribution of inhaled fluorescent magnetic nanoparticles in the mice. *Journal of Occupational Health* **50,** 1-6.

47.   Pauluhn, J., Hahn, A., and Spielmann, H. (2008). Assessment of early acute lung injury in rats exposed to aerosols of consumer products: Attempt to disentangle the "Magic nano" Conundrum. *Inhalation Toxicology* **20,** 1245-1262.

48.   Li, C. M., Taneda, S., Watanabe, G., Ito, Y., Nakajima, T., Taya, K., and Suzuki, A. (2008). Effects of nanoparticle enriched diesel exhaust on pregnancy in f344 rats. *Biology of Reproduction* **Special issue S1,** 134-5.

49.   Hahn, A., and Pauluhn, J. (2008). Assessment of early acute lung injury in rats exposed to aerosols of 'magic nano' sealing sprays. *Toxicology Letters* **180,** S55-S55.

50.   Shwe, T. T. W., Mitsushima, D., Yamamoto, S., Fujitani, Y., Funabashi, T., Hirano, S., and Fujimaki, H. (2008). Neurotoxic effect of nanoparticle-rich diesel exhaust in the mouse olfactory bulb. *Toxicology Letters* **180,** S206-S206.

51.   Alessandrini, F., Semmler-Behnke, M., Jakob, T., Schulz, H., Behrendt, H., and Kreyling, W. (2008). Total and regional deposition of ultrafine particles in a mouse model of allergic inflammation of the lung. *Inhal Toxicol* **20,** 585-93.

52.   Mortensen, L. J., Oberdorster, G., Pentland, A. P., and Delouise, L. A. (2008). In vivo skin penetration of quantum dot nanoparticles in the murine model: The effect of uvr. *Nano Lett* **8,** 2779-87.

53.   Choi, K., Lee, S., Youn, K., Yu, K., Choi, E., Ahn, S., and Lee, S. (2008). Skin permeation of nanoparticles by magnetophoresis in hairless mouse skin. *Journal of Investigative Dermatology* **128,** 651.

54.   Kim, Y. S., Kim, J. S., Cho, H. S., Rha, D. S., Kim, J. M., Park, J. D., Choi, B. S., Lim, R., Chang, H. K., Chung, Y. H., Kwon, I. H., Jeong, J., Han, B. S., and Yu, I. J. (2008). Twenty-

eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in sprague-dawley rats. *Inhalation Toxicology* **20,** 575-583.

55.   Cha, K., Hong, H. W., Choi, Y. G., Lee, M. J., Park, J. H., Chae, H. K., Ryu, G., and Myung, H. (2008). Comparison of acute responses of mice livers to short-term exposure to nano-sized or micro-sized silver particles. *Biotechnology Letters* **30,** 1893-1899.

56.   So, S. J., Jang, I. S., and Han, C. S. (2008). Effect of micro/nano silica particle feeding for mice. *Journal of Nanoscience and Nanotechnology* **8,** 5367-5371.

57.   Wang, B., Feng, W. Y., Wang, M., Wang, T. C., Gu, Y. Q., Zhu, M. T., Ouyang, H., Shi, J. W., Zhang, F., Zhao, Y. L., Chai, Z. F., Wang, H. F., and Wang, J. (2008). Acute toxicological impact of nano- and submicro-scaled zinc oxide powder on healthy adult mice. *Journal of Nanoparticle Research* **10,** 263-276.

58.   Park, H. S., Ahn, J., and Kwak, H. S. (2008). Effect of nano-calcium-enriched milk on calcium metabolism in ovariectomized rats. *Journal of Medicinal Food* **11,** 454-459.

59.   Fabian, E., Landsiedel, R., Ma-Hock, L., Wiench, K., Wohlleben, W., and van Ravenzwaay, B. (2008). Tissue distribution and toxicity of intravenously administered titanium dioxide nanoparticles in rats. *Archives of Toxicology* **82,** 151-157.

60.   Sugibayashi, K., Todo, H., and Kimura, E. (2008). Safety evaluation of titanium dioxide nanoparticles by their absorption and elimination profiles. *J Toxicol Sci* **33,** 293-8.

61.   Sonavane, G., Tomoda, K., and Makino, K. (2008). Biodistribution of colloidal gold nanoparticles after intravenous administration: Effect of particle size. *Colloids Surf B Biointerfaces* **66,** 274-80.

62.   Lin, P., Chen, J. W., Chang, L. W., Wu, J. P., Redding, L., Chang, H., Yeh, T. K., Yang, C. S., Tsai, M. H., Wang, H. J., Kuo, Y. C., and Yang, R. S. H. (2008). Computational and ultrastructural toxicology of a nanoparticle, quantum dot 705, in mice. *Environmental Science & Technology* **42,** 6264-6270.

63.   Lei, R. H., Wu, C. Q., Yang, B. H., Ma, H. Z., Shi, C., Wang, Q. J., Wang, Q. X., Yuan, Y., and Liao, M. Y. (2008). Integrated metabolomic analysis of the nano-sized copper particle-induced hepatotoxicity and nephrotoxicity in rats: A rapid in vivo screening method for nanotoxicity. *Toxicology and Applied Pharmacology* **232,** 292-301.

64.   Tang, J. L., Xiong, L., Wang, S., Wang, J. Y., Liu, L., Li, J. A., Wan, Z. Y., and Xi, T. F. (2008). Influence of silver nanoparticles on neurons and blood-brain barrier via subcutaneous injection in rats. *Applied Surface Science* **255,** 502-504.

65.   Balakrishna, S., Fahmy, B., Lomnicki, S., Dellinger, B., Ahlert, T., You, D., and Cormier, S. A. (2008). Anyl 338-combustion generated nanoparticles: Pro-inflammatory effects and role of oxidative stress in neonatal rat exposure models. *Abstracts of Papers of the American Chemical Society* **236**.

66.   Li, C. M., Taneda, S. J., Taya, K., Watanabe, G., Nakajima, T., and Suzuki, A. K. (2008). In utero exposure to nanoparticle-rich diesel exhaust suppressed testicular function in immature male rats. *Toxicology Letters* **180,** S189-S189.

67.   Milto, I. V., Kalugina, Y. F., and Magayeva, A. A. (2008). Biochemical plasma parameters in rats during intravenous injection of magnetite nanopowder. *Gigiena i Sanitariya***,** 42-44.

68.   Nikitin, A., Wang, Y., and Giannelis, E. (2008). In vivo toxicity studies of nanoparticles. *Toxicology Letters* **180,** S222-S222.

69.   Taneda, S., Li, C., Noya, Y., Seki, K. I., Ohkura, K., Yamaki, K., Yoshino, S., and Suzuki, A. K. (2008). Carbon nanoparticles enhance vasodilatory activity of thoracic artery induced by acetylcoline in rats. *Toxicology Letters* **180,** S226-S227.

70.   Tulinska, J., Liskova, A., Kuricova, M., Neubauerova, E., Kovacikova, Z., and Tatrai, E. (2008). Assessment of immunotoxicity of nio nanoparticles in rats. *Toxicology Letters* **180,** S227-S227.

71.   Harper, S., Usenko, C., Hutchison, J. E., Maddux, B. L. S., and Tanguay, R. L. (2008). In vivo biodistribution and toxicity depends on nanomaterial composition, size, surface functionalisation and route of exposure. *Journal of Experimental Nanoscience* **3,** 195-206.

72.   Kemp, S. J., Thorley, A. J., Gorelik, J., Seckl, M. J., O'Hare, M. J., Arcaro, A., Korchev, Y., Goldstraw, P., and Tetley, T. D. (2008). Immortalization of human alveolar epithelial cells to investigate nanoparticle uptake. *Am J Respir Cell Mol Biol* **39,** 591-7.

73.   Journeay, W. S., Suri, S. S., Moralez, J. G., Fenniri, H., and Singh, B. (2008). Low inflammatory activation by self-assembling rosette nanotubes in human calu-3 pulmonary epithelial cells. *Small* **4,** 817-23.

74.   Rotoli, B. M., Bussolati, O., Bianchi, M. G., Barilli, A., Balasubramanian, C., Bellucci, S., and Bergamaschi, E. (2008). Non-functionalized multi-walled carbon nanotubes alter the paracellular permeability of human airway epithelial cells. *Toxicology Letters* **178,** 95-102.

75.   Panessa-Warren, B. J., Warren, J. B., Maye, M. M., Van der Lelie, D., Gang, O., Wong, S. S., Ghebrehiwet, B., Tortora, G. T., and Misewich, J. A. (2008). Human epithelial cell processing of carbon and gold nanoparticles. *International Journal of Nanotechnology* **5,** 55-91.

76.   Simon-Deckers, A., Gouget, B., Mayne-L'Hermite, M., Herlin-Boime, N., Reynaud, C., and Carriere, M. (2008). In vitro investigation of oxide nanoparticle and carbon nanotube toxicity and intracellular accumulation in a549 human pneumocytes. *Toxicology* **253,** 137-146.

77.   Karlsson, H. L., Cronholm, P., Gustafsson, J., and Moller, L. (2008). Copper oxide nanoparticles are highly toxic: A comparison between metal oxide nanoparticles and carbon nanotubes. *Chemical Research in Toxicology* **21,** 1726-1732.

78.   Huang, C. C., Aronstam, R. S., Chen, D. R., and Huang, Y. W. (2008). Zinc oxide nanoparticles induce oxidative stress and alter calcium homeostasis in human bronchial epithelial cells (beas-2b). *Free Radical Biology and Medicine* **45,** S31-S31.

79.   Xia, T., Kovochich, M., Liong, M., Madler, L., Gilbert, B., Shi, H. B., Yeh, J. I., Zink, J. I., and Nel, A. E. (2008). Comparison of the mechanism of toxicity of zinc oxide and cerium oxide nanoparticles based on dissolution and oxidative stress properties. *Acs Nano* **2,** 2121-2134.

80.   Chen, E., Ruvalcaba, M., Araujo, L., Chapman, R., and Chin, W. C. (2008). Ultrafine titanium dioxide nanoparticles induce cell death in human bronchial epithelial cells. *Journal of Experimental Nanoscience* **3,** 171-183.

81.   Moss, O. R. (2008). Insights into the health effects of nanoparticles: Why numbers matter. *International Journal of Nanotechnology* **5,** 3-14.

82.   Mroz, R. M., Schins, R. P. F., Li, H., Jimenez, L. A., Drost, E. M., Holownia, A., MacNee, W., and Donaldson, K. (2008). Nanoparticle-driven DNA damage mimics irradiation-related carcinogenesis pathways. *Eur Respir J* **31,** 241-51.

83.   Yang, H., Liu, C., Yang, D., and Zhang, H. (2008). [study of c-zno composite nanoparticles on viability inhibition and DNA damage of mouse embryo fibroblasts]. *Wei Sheng Yan Jiu* **37,** 12-5.

84.   Jacobsen, N. R., Pojana, G., White, P., Moller, P., Cohn, C. A., Korsholm, K. S., Vogel, U., Marcomini, A., Loft, S., and Wallin, H. (2008). Genotoxicity, cytotoxicity, and reactive oxygen species induced by single-walled carbon nanotubes and c-60 fullerenes in the fe1-muta (tm) mouse lung epithelial cells. *Environmental and Molecular Mutagenesis* **49,** 476-487.

85.   Paur, H. R., Mulhopt, S., Weiss, C., and Diabate, S. (2008). In vitro exposure systems and bioassays for the assessment of toxicity of nanoparticles to the human lung. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety* **3,** 319-329.

86.   Holder, A. L., Lucas, D., Goth-Goldstein, R., and Koshland, C. P. (2008). Cellular response to diesel exhaust particles strongly depends on the exposure method. *Toxicol Sci* **103,** 108-15.

87.   Sayes, C. M., and Warheit, D. B. (2008). An in vitro investigation of the differential cytotoxic responses of human and rat lung epithelial cell lines using tio2 nanoparticles. *International Journal of Nanotechnology* **5,** 15-29.

88.   Constant, S., Huang, S., Derouette, J. P., and Wiszniewski, L. (2008). Mucilair: A novel in vitro human 3d airway epithelium model for assessing the potential hazard of nanoparticles and chemical compounds. *Toxicology Letters* **180,** S233-S233.

89.   Stoker, E., Purser, F., Kwon, S., Park, Y.-B., and Lee, J. S. (2008). Alternative estimation of human exposure of single-walled carbon nanotubes using three-dimensional tissue-engineered human lung. *Int J Toxicol* **27,** 441-8.

90.   Zhang, L. W., Yu, W. W., Colvin, V. L., and Monteiro-Riviere, N. A. (2008). Biological interactions of quantum dot nanoparticles in skin and in human epidermal keratinocytes. *Toxicology and Applied Pharmacology* **228,** 200-211.

91.   Zhang, L. W., and Monteiro-Riviere, N. A. (2008). Assessment of quantum dot penetration into intact, tape-stripped, abraded and flexed rat skin. *Skin Pharmacol Physiol* **21,** 166-80.

92.   Rouse, J. G., Haslauer, C. M., Loboa, E. G., and Monteiro-Riviere, N. A. (2008). Cyclic tensile strain increases interactions between human epidermal keratinocytes and quantum dot nanoparticles. *Toxicology in Vitro* **22,** 491-497.

93.   Sonavane, G., Tomoda, K., Sano, A., Ohshima, H., Terada, H., and Makino, K. (2008). In vitro permeation of gold nanoparticles through rat skin and rat intestine: Effect of particle size. *Colloids and Surfaces B-Biointerfaces* **65,** 1-10.

94.   Wang, S. G., Lu, W. T., Tovmachenko, O., Rai, U. S., Yu, H. T., and Ray, P. C. (2008). Challenge in understanding size and shape dependent toxicity of gold nanomaterials in human skin keratinocytes. *Chemical Physics Letters* **463,** 145-149.

95.   Zeni, O., Palumbo, R., Bernini, R., Zeni, L., Sarti, M., and Scarfi, M. R. (2008). Cytotoxicity investigation on cultured human blood cells treated with single-wall carbon nanotubes. *Sensors* **8,** 488-499.

96.   Pacurari, M., Yin, X. J., Ding, M., Leonard, S. S., Schwegler-Berry, D., Ducatman, B. S., Chirila, M., Endo, M., Castranova, V., and Vallyathan, V. (2008). Oxidative and molecular interactions of multi-wall carbon nanotubes (mwcnt) in normal and malignant human mesothelial cells. *Nanotoxicology* **2,** 155-170.

97.   Pacurari, M., Yin, X. J., Zhao, J., Ding, M., Leonard, S. S., Schwegler-Berry, D., Ducatman, B. S., Sbarra, D., Hoover, M. D., Castranova, V., and Vallyathan, V. (2008). Raw single-wall carbon nanotubes induce oxidative stress and activate mapks, ap-1, nf-kappab, and akt in normal and malignant human mesothelial cells. *Environ Health Perspect* **116,** 1211-7.

98.   Jin, H., Heller, D. A., and Strano, M. S. (2008). Single-particle tracking of endocytosis and exocytosis of single-walled carbon nanotubes in nih-3t3 cells. *Nano Lett* **8,** 1577-85.

99.   Bonafe, R., Bardini, P., Bussi, S., and Maiochi, A. (2008). Cytotoxic effects of carbon nanotubes (cnts) and fullerenes on human fibroblasts: Choosing the best suspension method. *Toxicology Letters* **180,** S220-S221.

100.   Lai, J. C. K., Lai, M. B., Jandhyam, S., Dukhande, V. V., Bhushan, A., Daniels, C. K., and Leung, S. W. (2008). Exposure to titanium dioxide and other metallic oxide nanoparticles induces cytotoxicity on human neural cells and fibroblasts. *International Journal of Nanomedicine* **3,** 533-545.

101.   Jin, C. Y., Zhu, B. S., Wang, X. F., and Lu, Q. H. (2008). Cytotoxicity of titanium dioxide nanoparticles in mouse fibroblast cells. *Chemical Research in Toxicology* **21,** 1871-1877.

102.   Lorenz, M. R., Kohnle, M.-V., Dass, M., Walther, P., Hocherl, A., Ziener, U., Landfester, K., and Mailander, V. (2008). Synthesis of fluorescent polyisoprene nanoparticles and their uptake into various cells. *Macromol Biosci* **8,** 711-27.

103.   Wan, R., Mo, Y. Q., Zhang, X., Chien, S. F., Tollerud, D. J., and Zhang, Q. W. (2008). Matrix metalloproteinase-2 and-9 are induced differently by metal nanoparticles in human monocytes: The role of oxidative stress and protein tyrosine kinase activation. *Toxicology and Applied Pharmacology* **233,** 276-285.

104.   Rothen-Rutishauser, B., Muller, L., Blank, F., Brandenberger, C., Muhlfeld, C., and Gehr, P. (2008). A newly developed in vitro model of the human epithelial airway barrier to study the toxic potential of nanoparticles. *Altex-Alternativen Zu Tierexperimenten* **25,** 191-196.

105.   Goya, G. F., Marcos-Campos, I., Fernandez-Pacheco, R., Saez, B., Godino, J., Asin, L., Lambea, J., Tabuenca, P., Mayordomo, J. I., Larrad, L., Ibarra, M. R., and Tres, A. (2008). Dendritic cell uptake of iron-based magnetic nanoparticles. *Cell Biol Int* **32,** 1001-5.

106.   Koike, E., Takano, H., Inoue, K., Yanagisawa, R., and Kobayashi, T. (2008). Carbon black nanoparticles promote the maturation and function of mouse bone marrow-derived dendritic cells. *Chemosphere* **73,** 371-376.

107.   Jos, A., Pichardo, S., Puerto, M., Moreno, I. M., Camean, A. M., Sanchez, E., and Grilo, A. (2008). Toxic effects induced by carbon nanotubes on the intestinal human cell line caco-2. *Toxicology Letters* **180,** S224-S224.

108.   Lai, Y. R., Chiang, P. C., Blom, J. D., Li, N., Shevlin, K., Brayman, T. G., Hu, Y. D., Selbo, J. G., and Hu, L. G. (2008). Comparison of in vitro nanoparticles uptake in various cell lines and in vivo pulmonary cellular transport in intratracheally dosed rat model. *Nanoscale Research Letters* **3,** 321-329.

109.   Dey, S., Bakthavatchalu, V., Tseng, M. T., Wu, P., Florence, R. L., Grulke, E. A., Yokel, R. A., Dhar, S. K., Yang, H. S., Chen, Y. M., and Clair, D. K. S. (2008). Interactions between sirt1 and ap-1 reveal a mechanistic insight into the growth promoting properties of alumina (al2o3) nanoparticles in mouse skin epithelial cells. *Carcinogenesis* **29,** 1920-1929.

110.   Myllynen, P. K., Loughran, M. J., Howard, C. V., Sormunen, R., Walsh, A. A., and Vahakangas, K. H. (2008). Kinetics of gold nanoparticles in the human placenta. *Reproductive Toxicology* **26,** 130-137.

111.   Komatsu, T., Tabata, M., Kubo-Irie, M., Shimizu, T., Suzuki, K., Nihei, Y., and Takeda, K. (2008). The effects of nanoparticles on mouse testis leydig cells in vitro. *Toxicology in Vitro* **22,** 1825-1831.

112.   Liu, J., and Hopfinger, A. J. (2008). Identification of possible sources of nanotoxicity from carbon nanotubes inserted into membrane bilayers using membrane interaction quantitative structure--activity relationship analysis. *Chem Res Toxicol* **21,** 459-66.

113.   Salvador-Morales, C., Basiuk, E. V., Basiuk, V. A., Green, M. L. H., and Sim, R. B. (2008). Effects of covalent functionalization on the biocompatibility characteristics of multi-walled carbon nanotubes. *J Nanosci Nanotechnol* **8,** 2347-56.

114.   Sereemaspun, A., Rojanathanes, R., and Wiwanitkit, V. (2008). Effect of gold nanoparticle on renal cell: An implication for exposure risk. *Ren Fail* **30,** 323-5.

115.   Alekseenko, A. V., Waseem, T. V., and Fedorovich, S. V. (2008). Ferritin, a protein containing iron nanoparticles, induces reactive oxygen species formation and inhibits glutamate uptake in rat brain synaptasomes. *Brain Research* **1241,** 193-200.

116.   Wu, W.-H., Sun, X., Yu, Y.-P., Hu, J., Zhao, L., Liu, Q., Zhao, Y.-F., and Li, Y.-M. (2008). Tio2 nanoparticles promote beta-amyloid fibrillation in vitro. *Biochem Biophys Res Commun* **373,** 315-8.

117.   Gheshlaghi, Z. N., Riazi, G. H., Ahmadian, S., Ghafari, M., and Mahinpour, R. (2008). Toxicity and interaction of titanium dioxide nanoparticles with microtubule protein. *Acta Biochim Biophys Sin (Shanghai)* **40,** 777-82.

118.   Malarkey, E. B., Reyes, R. C., Zhao, B., Haddon, R. C., and Parpura, V. (2008). Water soluble single-walled carbon nanotubes inhibit stimulated endocytosis in neurons. *Nano Lett* **8,** 3538-42.

119.   Xu, G., Yong, K.-T., Roy, I., Mahajan, S. D., Ding, H., Schwartz, S. A., and Prasad, P. N. (2008). Bioconjugated quantum rods as targeted probes for efficient transmigration across an in vitro blood-brain barrier. *Bioconjug Chem* **19,** 1179-85.

120.   Zhang, Y., Yang, M., Portney, N. G., Cui, D. X., Budak, G., Ozbay, E., Ozkan, M., and Ozkan, C. S. (2008). Zeta potential: A surface electrical characteristic to probe the interaction of nanoparticles with normal and cancer human breast epithelial cells. *Biomedical Microdevices* **10,** 321-328.

121.   Wang, C.-C., Lee, C.-W., Huang, C.-Y., Lin, J.-Y., Wei, P.-K., and Lee, C.-H. (2008). Observation of nanoparticle internalization on cellular membranes by using noninterferometric widefield optical profilometry. *Appl Opt* **47,** 2458-64.

122.   Rogers, E. J., Hsieh, S. F., Organti, N., Schmidt, D., and Bello, D. (2008). A high throughput in vitro analytical approach to screen for oxidative stress potential exerted by nanomaterials using a biologically relevant matrix: Human blood serum. *Toxicology in Vitro* **22,** 1639-1647.

123.   Vamanu, C. I., Cimpan, M. R., Hol, P. J., Sornes, S., Lie, S. A., and Gjerdet, N. R. (2008). Induction of cell death by tio2 nanoparticles: Studies on a human monoblastoid cell line. *Toxicology in Vitro* **22,** 1689-1696.

124.   Soto, K. F., Murr, L. E., and Garza, K. M. (2008). Cytotoxic responses and potential respiratory health effects of carbon and carbonaceous nanoparticulates in the paso del norte airshed environment. *Int J Environ Res Public Health* **5,** 12-25.

125.   Suzuki, K. (2008). Methodological research on nanoparticle characterization for environment and health effects. *Bunseki Kagaku* **57,** 575-576.

126.   Asharani, P. V., Hande, M. P., and Valiyaveettil, S. (2008). Inor 818-toxicity of silver nanoparticles in human cells. *Abstracts of Papers of the American Chemical Society* **236,** 818-INOR.

127.   Bandyopadhyay, D., Wallen, R., Bercea, P., Ye, B. R., Sudakar, C., Regmi, R., Lawes, G., and Bandyopadhyay, K. (2008). Anyl 94-toxic potential of metal nanoparticles on yeast cells. *Abstracts of Papers of the American Chemical Society* **236**.

128.   Chen, L., Zhang, H., Bromberg, L., Smith, K. A., Rutledge, G. C., and Hatton, T. A. (2008). I&ec 20-functionalized magnetic nanoparticles and nanofibers for protection against chemical and biological toxicants. *Abstracts of Papers of the American Chemical Society* **236,** 20-IEC.

129.   Fahmy, B., Balakrishna, S., and Cormier, S. (2008). Assessment of pulmonary toxicity associated with the exposure to metal oxide nanoparticles in-vitro: Copper oxide induces oxidative stress and a pro-inflammatory response in human epithelial cells. *Free Radical Biology and Medicine* **45,** S45-S45.

130.   Hackley, V. A. (2008). Anyl 201-nanoparticle reference materials: Enablers for technology development and the assessment of environmental, health and safety impact. *Abstracts of Papers of the American Chemical Society* **236,** 201-ANYL.

131.   Lee, J. A., Krogman, K. C., Ma, M., Rutledge, G. C., and Hammond, P. T. (2008). Pmse 273-reactive tio2-coated silicone nanofibers using layer-by-layer (lbl) deposition and their

photocatalytic activities for degradation of toxic chemicals. *Abstracts of Papers of the American Chemical Society* **236,** 273-PMSE.

132.   Maddux, B., Harper, S. L., Tanguay, R. L., and Hutchison, J. E. (2008). Anyl 266-addressing environmental, health and safety challenges in nanomaterials research through green nanoscience. *Abstracts of Papers of the American Chemical Society* **236,** 266-ANYL.

133.   Richter, V., Potthoff, A., Pompe, W., Gelinsky, M., Ikonomidou, H., Bastian, S., Schirmer, K., Scholz, S., and Hofinger, J. (2008). Evaluation of health risks of nano- and microparticles. *Powder Metallurgy* **51,** 8-9.

134.   Stoeger, T., Schmid, O., and Schulz, H. (2008). Anyl 337-toxicity of combustion-derived nanoparticles: A product of particle's innate oxidative potency and metabolic activation of organic compounds. *Abstracts of Papers of the American Chemical Society* **236**.

135.   Tarasevich, B. J., Thrall, B. D., Waters, K. M., Karin, N. J., and Zangar, R. C. (2008). Anyl 290-studies on the effects of particle size on the toxicology of nanoparticles. *Abstracts of Papers of the American Chemical Society* **236**.

136.   Warheit, D. B. (2008). Anyl 269-influence of surface reactivity on nanoparticle pulmonary toxicity in vivo: The case of nanoquartz and nanotitanium dioxide particle-types. *Abstracts of Papers of the American Chemical Society* **236**.

137.   Liao, C. M., Chiang, Y. H., and Chio, C. P. (2008). Model-based assessment for human inhalation exposure risk to airborne nano/fine titanium dioxide particles. *Science of the Total Environment* **407,** 165-177.

138.   Ok, Z. D., Benneyan, J. C., and Isaacs, J. A. (2008). Risk analysis modeling of production costs and occupational health exposure of single-wall carbon nanotube manufacturing. *Journal of Industrial Ecology* **12,** 411-434.

139.   Xi, J., Longest, P. W., and Martonen, T. B. (2008). Effects of the laryngeal jet on nano- and microparticle transport and deposition in an approximate model of the upper tracheobronchial airways. *J Appl Physiol* **104,** 1761-77.

140.   Zhang, Z., Kleinstreuer, C., and Kim, C. S. (2008). Airflow and nanoparticle deposition in a 16-generation tracheobronchial airway model. *Ann Biomed Eng* **36,** 2095-110.

141.   Decuzzi, P., and Ferrari, M. (2008). Design maps for nanoparticles targeting the diseased microvasculature. *Biomaterials* **29,** 377-84.

142.   Wong-Ekkabut, J., Baoukina, S., Triampo, W., Tang, I. M., Tieleman, D. P., and Monticelli, L. (2008). Computer simulation study of fullerene translocation through lipid membranes. *Nat Nanotechnol* **3,** 363-8.

143.   Nasterlack, M., Zober, A., and Oberlinner, C. (2008). Considerations on occupational medical surveillance in employees handling nanoparticles. *Int Arch Occup Environ Health* **81,** 721-6.

144.   Schulte, P. A., Trout, D., Zumwalde, R. D., Kuempel, E., Geraci, C. L., Castranova, V., Mundt, D. J., Mundt, K. A., and Halperin, W. E. (2008). Options for occupational health surveillance of workers potentially exposed to engineered nanoparticles: State of the science. *Journal of Occupational and Environmental Medicine* **50,** 517-526.

145.   Schulte, P., Geraci, C., Zumwalde, R., Hoover, M., and Kuempel, E. (2008). Occupational risk management of engineered nanoparticles. *J Occup Environ Hyg* **5,** 239-49.

146.   Schulte, P., Geraci, C., Zumwalde, R., Hoover, M., Castranova, V., Kuempel, E., Murashov, V., Vainio, H., and Savolainen, K. (2008). Sharpening the focus on occupational safety and health in nanotechnology. *Scandinavian Journal of Work Environment & Health* **34,** 471-478.

147.   Schneider, T. (2008). Role of occupational hygiene research in the control of occupational health risks from engineered nanoparticles. *Scandinavian Journal of Work Environment & Health* **34,** 407-409.

148.   O'Brien, N., and Cummins, E. (2008). Recent developments in nanotechnology and risk assessment strategies for addressing public and environmental health concerns. *Human and Ecological Risk Assessment* **14,** 568-592.

149.   Osman, T. M. (2008). Environmental, health, and safety considerations for producing nanomaterials. *Jom* **60,** 14-17.

150.   Bourne, J., and Walton, T. (2008). Nanotechnology - safety, health and environmental issues. *Surface Coatings International* **91,** 21-30.

151.   Conti, J. A., Killpack, K., Gerritzen, G., Huang, L., Mircheva, M., Delmas, M., Harthorn, B. H., Appelbaum, R. P., and Holden, P. A. (2008). Health and safety practices in the nanomaterials workplace: Results from an international survey. *Environmental Science & Technology* **42,** 3155-3162.

152.   Helland, A., Scheringer, M., Siegrist, M., Kastenholz, H. G., Wiek, A., and Scholz, R. W. (2008). Risk assessment of engineered nanomaterials: A survey of industrial approaches. *Environ Sci Technol* **42,** 640-6.

153.   Schmid, K., and Riediker, M. (2008). Use of nanoparticles in swiss industry: A targeted survey. *Environ Sci Technol* **42,** 2253-60.

154.   Casals, E., Vazquez-Campos, S., Bastus, N. G., and Puntes, V. (2008). Distribution and potential toxicity of engineered inorganic nanoparticles and carbon nanostructures in biological systems. *Trac-Trends in Analytical Chemistry* **27,** 672-683.

155.   Choi, S. J., Oh, J. M., and Choy, J. H. (2008). Human-related application and nanotoxicology of inorganic particles: Complementary aspects. *Journal of Materials Chemistry* **18,** 615-620.

156.   Durnev, A. D. (2008). Toxicology of nanoparticles. *Bull Exp Biol Med* **145,** 72-4.

157.   Morimoto, Y., and Tanaka, I. (2008). [effects of nanoparticles on humans]. *Sangyo Eiseigaku Zasshi* **50,** 37-48.

158.   Zholdakova, Z. I., Sinitsina, O. O., and Kharchevnikova, N. V. (2008). General and specific aspects of the toxic properties of nanoparticles and other chemical substances in the context of classical toxicology. *Gigiena i Sanitariya***,** 12-16.

159.   Hirose, A., and Hirano, S. (2008). Health effects of nanoparticles and nanomaterials (iii). *Nippon Eiseigaku Zasshi* **63,** 739-45.

160.   Lai, C., Lin, M., Loh, C., Chen, C., Chien, W., Jaakkola, J. J. K., and Liou, S. (2008). Investigation of health effects in nanotechnological industry. *Epidemiology* **19,** S149-S149.

161.   Stern, S. T., and McNeil, S. E. (2008). Nanotechnology safety concerns revisited. *Toxicol Sci* **101,** 4-21.

162.   Chaudhry, Q., Scotter, M., Blackburn, J., Ross, B., Boxall, A., Castle, L., Aitken, R., and Watkins, R. (2008). Applications and implications of nanotechnologies for the food sector. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* **25,** 241-58.

163.   Richter, V., and Bastian, S. (2008). Evaluation of health effects of the use of nanoparticles a contribution on sustainable development of nanotechnology. *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety* **3,** 332-338.

164.   Siegrist, M., Stampfli, N., Kastenholz, H., and Keller, C. (2008). Perceived risks and perceived benefits of different nanotechnology foods and nanotechnology food packaging. *Appetite* **51,** 283-90.

165.   Hansen, S. F., Michelson, E. S., Kamper, A., Borling, P., Stuer-Lauridsen, F., and Baun, A. (2008). Categorization framework to aid exposure assessment of nanomaterials in consumer products. *Ecotoxicology* **17,** 438-47.

166.   Groce, D. F. (2008). Hazards demand proper protection. *Occup Health Saf* **77,** 74, 76, 78.

167.   Hansen, S. F., Maynard, A., Baun, A., and Tickner, J. A. (2008). Late lessons from early warnings for nanotechnology. *Nat Nanotechnol* **3,** 444-7.

168.   Jahnen-Dechent, W., and Simon, U. (2008). Function follows form: Shape complementarity and nanoparticle toxicity. *Nanomed* **3,** 601-3.

169.   Lewinski, N. (2008). Nanomaterials: What are the environmental and health impacts? *Chemical Engineering Progress* **104,** 37-40.

170.   Prosie, F., Lesage, F. X., and Deschamps, F. (2008). Nanoparticles: Structures, utilizations and health impacts. *Presse Medicale* **37,** 1431-1437.

171.   Warheit, D. B., Sayes, C. M., Reed, K. L., and Swain, K. A. (2008). Health effects related to nanoparticle exposures: Environmental, health and safety considerations for assessing hazards and risks. *Pharmacology & Therapeutics* **120,** 35-42.

172.   Kuzma, J., Romanchek, J., and Kokotovich, A. (2008). Upstream oversight assessment for agrifood nanotechnology: A case studies approach. *Risk Anal* **28,** 1081-98.

173.   Card, J. W., Zeldin, D. C., Bonner, J. C., and Nestmann, E. R. (2008). Pulmonary applications and toxicity of engineered nanoparticles. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **295,** L400-L411.

174.   Zhang, T., and Tang, M. (2008). [advances of study on inhalation toxicity of nanoparticles]. *Wei Sheng Yan Jiu* **37,** 633-6.

175.   Baroli, B. (2008). Nanoparticles and skin penetration. Are there any potential toxicological risks? *Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal of Consumer Protection and Food Safety* **3,** 330-331.

176.   Helland, A., Wick, P., Koehler, A., Schmid, K., and Som, C. (2008). Reviewing the environmental and human health knowledge base of carbon nanotubes. *Cien Saude Colet* **13,** 441-52.

177.   Nielsen, G. D., Roursgaard, M., Jensen, K. A., Poulsen, S. S., and Larsen, S. T. (2008). In vivo biology and toxicology of fullerenes and their derivatives. *Basic Clin Pharmacol Toxicol* **103,** 197-208.

178.   Chen, X., and Schluesener, H. J. (2008). Nanosilver: A nanoproduct in medical application. *Toxicol Lett* **176,** 1-12.

179.   Panyala, N. R., Pena-Mendez, E. M., and Havel, J. (2008). Silver or silver nanoparticles: A hazardous threat to the environment and human health? *Journal of Applied Biomedicine* **6,** 117-129.

180.   Oberdorster, G. (2008). Potential adverse human health impacts of nanomaterials. *Chemical Research in Toxicology* **21,** 92.

181.   Kane, A. B. (2008). Environmental and human health impacts of nanomaterials. *Chemical Research in Toxicology* **21,** 89.

182.   Chen, L., Lee, J. C. M., and Li, H. (2008). Toxicity study of hydroxyapatite nanomaterials with different shape using osteoblast cell. *Chemical Research in Toxicology* **21,** 85.

183.   Nohynek, G. J., Dufour, E. K., and Roberts, M. S. (2008). Nanotechnology, cosmetics and the skin: Is there a health risk? *Skin Pharmacology and Physiology* **21,** 136-149.

184.   Li, N., Xia, T., and Nel, A. E. (2008). The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Radical Biology and Medicine* **44,** 1689-1699.

185.   Poma, A., and Di Giorgio, M. L. (2008). Toxicogenomics to improve comprehension of the mechanisms underlying responses of in vitro and in vivo systems to nanomaterials: A review. *Current Genomics* **9,** 571-585.

186.   Sequeira, R., Genaidy, A., Weckman, G., Shell, R., Karwowski, W., and Acosta-Leon, A. (2008). Health effects of nanomaterials: A critical appraisal approach and research to practice. *Human Factors and Ergonomics in Manufacturing* **18,** 293-341.

3. CONTACTS

For more information, please contact:

Measurement, exposure and control:

Delphine Bard (Analytical Sciences Unit):   Tel: 01298 218558
(delphine.bard@hsl.gov.uk)

Nick Vaughan (Personal Protection Equipment Section):   Tel: 01298 218329
(nick.vaughan@hsl.gov.uk)

Health effects:

Rosemary Gibson (Occupational Hygiene Unit):   Tel: 01298 218675
rosemary.gibson@hsl.gov.uk

Gareth Evans (Occupational Hygiene Unit)   Tel: 01298 218410
(gareth.hsl.evans@hsl.gov.uk)