5 August 2005

Elton Humphery
Secretary
Senate Community Affairs References Committee
Parliament House
Canberra ACT 2600

Dear Mr Humphery

Attached is a submission presented in response to the invitation from the Senate Community Affairs References Committee for comments on matters relating to workplace exposure to toxic dust.

My objective is to present what is readily available in the published literature on risks of exposure to nanoparticles. My expertise is in conducting literature searches in the biomedical area. I have no background in the sciences related to nanotechnology, and do not attempt to interpret or appraise what the authors have written.

I present this submission in a purely private capacity, and my statements in no way represent the views of my employer, Sir Charles Gairdner Hospital.

The source materials discussed in this review have been selected from publicly-available databases. If required, I would be happy to provide either copies of the articles or further details of the review.

I look forward to your response.

Yours sincerely

Cecily Gilbert

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1. INTRODUCTION

This submission addresses the Inquiry's Term of Reference G:

> The potential of emerging technologies, including nanoparticles, to result in workplace related harm.

The submission comprises a descriptive summary of published literature and clinical trials on known, likely or possible risks of exposure to inhaled nanoparticles.

At the present time, nanoparticles in use are chiefly man-made from silicon, carbon, and metal oxides (including zinc dioxide and titanium dioxide). A useful summary of the health and environmental issues surrounding nanotechnology is available in a 2003 document "Nanotechnology implications in health and the environment" produced by the US National Science Foundation. This is a chapter reporting a joint workshop of the NSF and the US Environment Protection Agency. The full report can be found online at http://es.epa.gov/ncer/publications/nano/nanotechnology4-20-04.pdf

It is difficult at this stage to isolate studies which discuss only workplace exposure to nanoparticles. Many articles group together effects of biological, industrial or environmental exposure. In assessing workplace related harm, it is valid to include environmental exposure, since this is relevant to a range of occupations, including outdoor work and transport industries.

A bibliography of relevant articles is included.

2. METHODOLOGY

In the time frame available, it has not been possible to conduct a comprehensive literature search on this topic. The published material about nanotechnology is scattered across a wide range of disciplines including biomedicine, biotechnology, biochemistry, biophysics, engineering, aerospace, pharmaceutical science, medicine, environmental science and toxicology. A thorough search would require 6-8 weeks of dedicated time, which has not been available prior to the Committee's deadline. In addition, much of the nanotechnology research is being conducted by privately-funded organisations, hence most of that information is unavailable, being commercial-in-confidence or protected by patent.

The scoping search for published journal articles was conducted during July and early August 2005. Sources searched were:

- Medline (PubMed) 1966 – 2005 July
- Embase 1996-2005 July
- Cochrane Library of Systematic Reviews – searched on 4 August 2005
- BioMedCentral repository – searched on 2 August 2005
- PubMedCentral repository – searched on 2 August 2005.

Search terms were:
[nanobio* OR nanofilt* OR nanomanufact* OR nanopartic* OR nanotech*]
AND
[inhal* OR pulmon* OR respir*]
AND
[health* OR harm* OR risk* OR toxic*]

No systematic reviews were found; however, that is not surprising in a relatively young technology such as nanotechnology. The small pool of published articles considering health effects of nanoparticles dates basically from 2001, and has increased through 2004-05. Many of the research studies are based on mouse models or in vitro models of human airway.

In this sequence, journal articles are arranged in reverse chronological order.

3. ANNOTATED BIBLIOGRAPHY

Murr LE. Garza KM. Soto KF. Carrasco A. Powell TG. Ramirez DA. Guerrero PA. Lopez DA. Venzor III J.
Cytotoxicity assessment of some carbon nanotubes and related carbon nanoparticle aggregates and the implications for anthropogenic carbon nanotube aggregates in the environment.
International Journal of Environmental Research & Public Health. Vol. 2(1)(pp 31-42), 2005.
Compared the toxicity of single-wall carbon nanotubes and two different multi-wall carbon nanotubes with chrysotile asbestos nanotubes and black carbon nanoaggregates as toxicity standards. The results indicated a strong concentration relationship and toxicity for all the carbon nanotube materials tested relative to the asbestos nanotubes and black carbon. These results also raise concerns for manufactured carbon nanotube aggregates, and related fullerene nanoparticles.

Fortner JD. Lyon DY. Sayes CM. Boyd AM. Falkner JC. Hotze EM. Alemany LB. Tao YJ. Guo W. Ausman KD. Colvin VL. Hughes JB.
C_{60} in water: Nanocrystal formation and microbial response.
Environmental Science & Technology. Vol. 39(11)(pp 4307-4316), 2005. Date of Publication: 01 JUN 2005.
C_{60} spontaneously forms a stable aggregate with nanoscale dimensions; in solution these aggregates are crystalline in order. Concludes: "This work demonstrates the fact that the environmental fate, distribution, and biological risk associated with this important class of engineered nanomaterials will require a model that addresses not only the properties of bulk C_{60} but also that of the aggregate form generated in aqueous media."

Pandey R. Khuller GK.
Antitubercular inhaled therapy: Opportunities, progress and challenges.
Journal of Antimicrobial Chemotherapy. Vol. 55(4)(pp 430-435), 2005.
Describes research into development of nanoparticle systems for inhaled delivery of antitubercular drugs. Notes that "Several key issues such as patient education, cost of treatment, stability and large scale production of drug formulations, etc. need to be addressed before antitubercular inhaled therapy finds its way from theory to clinical reality".

Zhang Z. Kleinstreuer C. Donohue JF. Kim CS.
Comparison of micro- and nano-size particle depositions in a human upper airway model.
Journal of Aerosol Science. Vol. 36(2)(pp 211-233), 2005.
Studied the deposition and concentration rates for microparticles and nanoparticles under differing flow conditions for a human upper airway model. Found that depositions of both micro- and nano-size particles vary measurably; however, the deposition distributions are much more uniform for nanoparticles. The authors hypothesized that uniformly deposited nanoparticles of similar concentrations may have greater toxicity effects when compared to microparticles of the same material.

Hoet PH, Bruske-Hohlfeld I, Salata OV.
Nanoparticles - known and unknown health risks.
J Nanobiotechnology. 2004 Dec 8;2(1):12.
This detailed review discusses the mechanisms of nanoparticle entry into the body through skin, intestinal tract or lungs, and examines studies into the known and potential health risks associated with this. It concludes that, after entering the body, the distribution of nanoparticles is strongly related to the

surface characteristics of the particles. Recommendations therefore include establishing a database of health risks associated with nanoparticles of different sizes and composition. Contaminants in the particles, such as the metals present in nanotubes, should also be considered when assessing toxicity of nanomaterials.

Donaldson K, Stone V, Tran CL, Kreyling W, Borm PJ
Nanotoxicology.
Occup Environ Med. 2004 Sep;61(9):727-8.
This editorial briefly examines the risks of exposure to nanoparticles as production increases: this may occur during manufacture, application and waste management. It highlights the key role played by the particle surface: "The same size of particle may be very different in its ability to translocate or have [toxic effects] if its surface is altered chemically for special industrial or therapeutic application…Considering that surface modification is the fastest-growing market for bulk nanoparticle application, the various effects of these treatments on the toxicology of nanoparticles should be investigated."

Brouwer DH. Gijsbers JHJ. Lurvink MWM.
Personal exposure to ultrafine particles in the workplace: Exploring sampling techniques and strategies.
Annals of Occupational Hygiene. Vol. 48(5)(pp 439-453), 2004.
A workplace study of measurement techniques for exposure to ultrafine (less than 100nm) particles. The authors drew on earlier environmental and toxicological studies, proposing that measuring exposures against mass alone is not sufficient; it is also necessary to consider exposures against surface area and number concentration. Their results found that static measures of particulates may not give an accurate picture of individual exposure.

Borm PJA.
Particle toxicology: From coal mining to nanotechnology.
Zentralblatt fur Arbeitsmedizin, Arbeitsschutz und Ergonomie. Vol. 54(6)(pp 188-197), 2004.
Tracks the changes in context and priorities over time in studies of adverse effects of exposure to particles in industry. Inhaled particle effects are now known to be more extensive than lung inflammation, because they may provoke systemic responses, and also because they are thought to translocate to the blood and brain. Particle size has decreased to the ultra-fine range, leading to a need to develop knowledge on the role of surface and size in particle toxicity. One new area of occupational concern is the production of nano-size carrier systems for medical uses.

Borm PJ, Kreyling W
Toxicological hazards of inhaled nanoparticles--potential implications for drug delivery.
J Nanosci Nanotechnol. 2004 May;4(5):521-31.
This paper is a key review of the known effects of inhaled nanoparticles, including (i) direct effects on the central nervous system, (ii) their translocation from the lung into the bloodstream, and (iii) their capacity to invoke inflammatory responses in the lung with subsequent systemic effects. It contrasts this knowledge with the pursuit of solutions for nanoparticle drug delivery systems, and recommends that both research fields work together to investigate the link between nanoparticle characteristics (size & properties) and mechanisms of disease.

Murr LE. Esquivel EV. Bang JJ.
Characterization of nanostructure phenomena in airborne particulate aggregates and their potential for respiratory health effects.
Journal of Materials Science-Materials in Medicine. Vol. 15(3)(pp 237-247), 2004.
Studied nanoparticles in hundreds of airborne aggregates to identify their size and crystalline features. Found most airborne particulates were aggregates ranging from a few nanometres to a few microns, containing a few to thousands of nanocrystals. Concludes: "The potential for ultrafine airborne aggregates to fragment into hundreds or thousands of nanoparticulate components in human airways and act as toxic agents in deep lung tissue is demonstrated."

Dreher KL.
Health and environmental impact of nanotechnology: Toxicological assessment of manufactured nanoparticles.
Toxicological Sciences. Vol. 77(1)(pp 3-5), 2004.
Overview of issues in risk assessment of manufactured nanoparticles. Themes are: paucity of information on nanoparticle toxicity and exposure assessment; validity of extrapolating toxicity data from existing particulates to nanomaterials; and the unclear bio-persistence of single-wall carbon nanotubes which may cause significant workplace health problems.

Maynard AD, Baron PA, Foley M, Shvedova AA, Kisin ER, Castranova V.
Exposure to carbon nanotube material: aerosol release during the handling of unrefined single-walled carbon nanotube material.
J Toxicol Environ Health A. 2004 Jun 9;67(1):87-107.
A laboratory and field study which examined (I) the aerosol components released when single-walled carbon nanotube material was agitated, and (II) exposure to carbon nanotubes via inhalation or skin contact when handling unrefined nanotube materials. Found that fine particles of unrefined nanotube materials are released during agitation, while concentrations released during handling are low. Glove deposits were higher, estimated at between 0.2 mg and 6 mg per hand.

Warheit DB, Laurence BR, Reed KL, Roach DH, Reynolds GA, Webb TR
Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats.
Toxicol Sci. 2004 Jan;77(1):117-25. Epub 2003 Sep 26.
Comment in: Toxicol Sci. 2004 Jan;77(1):3-5.
Examined outcomes after instillation of single-wall carbon nanotubes into rat lungs, compared with control groups which were instilled with other particle types. Exposure to nanotubes at high doses caused death in ~15% of the experimental group, produced transient inflammatory and cell-damaging effects, and multifocal granulomas (this latter was found to be non-dose-dependent). Concludes that these variable results require there be further study of inhalation toxicity of carbon nanotubes, since their pulmonary effects do not follow the normal pattern seen with toxic dusts. The authors are affiliated with the DuPont laboratories in Wilmington, Delaware.

Lam CW, James JT, McCluskey R, Hunter RL
Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation.
Toxicol Sci. 2004 Jan;77(1):126-34. Epub 2003 Sep 26.
Comment in: Toxicol Sci. 2004 Jan;77(1):3-5.
Mice instilled with either differing doses of single-wall carbon nanotubes, or control particle samples, were examined for pulmonary effects. After 7 days, all nanotube products induced dose-dependent granulomas; inflammation was also present in some subjects. These results were more pronounced at 90 days, with inflammation and necrosis extending into alveolar septa. The authors conclude that on an equal-weight basis, nanotubes reaching the lungs are “much more toxic than carbon black, and can be more toxic than quartz”.

Bottini M, Magrini A, Bottini N, Bergamaschi A.
[Nanotubes and fullerenes: an overview of the possible environmental and biological impact of bio-nanotechnologies]. [Article in Italian]
Med Lav. 2003 Nov-Dec;94(6):497-505.

Emerich DF, Thanos CG
Nanotechnology and medicine.
Expert Opin Biol Ther. 2003 Jul;3(4):655-63.
Reviews the potential uses of nanotechnology for disease diagnosis and treatment. Possible developments include use of nanoparticles for diagnostic and screening purposes, artificial receptors, DNA sequencing using nanopores, manufacture of unique drug delivery systems, gene therapy

applications and the enablement of tissue engineering. Observes that nanoparticles display self-ordering and assembling behaviours not seen in macro-size objects.

Service RF
American Chemical Society meeting. Nanomaterials show signs of toxicity.
Science 2003 Apr 11;300(5617):243.
News item discussing the emerging findings of adverse effects of carbon nanotubes on pulmonary tissue in rodents.

O'Neill G.
The best drugs come in small packages.
New Scientist 2002 Sept 7th:19.
A news item reporting that 'nanomised'insulin taken by inhalation may have improved bioavailability over injected forms. (This item was cited in a Cochrane Library review comparing inhaled with injected insulin in diabetes mellitus.)

Videira MA. Botelho MF. Santos AC. Gouveia LF. Pedroso De Lima JJ. Almeida AJ.
Lymphatic uptake of pulmonary delivered radiolabelled solid lipid nanoparticles.
Journal of Drug Targeting. Vol. 10(8)(pp 607-613), 2002.
Studied the transport of inhaled radiolabelled solid lipid nanoparticles in rats, measured by gamma imaging up to 4 hours after inhalation. Results showed a significant uptake of the nanoparticles not only into lung but also into the lymphatic system, and a high rate of distribution in periaortic, axillar and inguinal lymph nodes.

Dickinson PA. Howells SW. Kellaway IW.
Novel nanoparticles for pulmonary drug administration.
Journal of Drug Targeting. Vol. 9(4)(pp 295-302), 2001.
Describes the production method for hydrophilic drug nanoparticles, testing two microemulsions. The process produced aerosols with spherical nanoparticles less than 300nm. The results suggest that a high fraction of the nanoparticles would be deposited (targeted) within the lung with the deposition being mainly in the alveoli.

Nemery B, Bast A, Behr J, Borm PJ, Bourke SJ, Camus PH, De Vuyst P, Jansen HM, Kinnula VL, Lison D, Pelkonen O, Saltini C.
Interstitial lung disease induced by exogenous agents: factors governing susceptibility.
Eur Respir J Suppl. 2001 Sep;32:30s-42s.
Reviews what is known of host susceptibility to interstitial lung disease from exposure to noxious agents. Factors include: delivery and persistence of the agent in the lung (which is governed by a range of physiological and genetic issues); genetic and acquired variations in cell and tissue defense systems, immunological sensitization, and propensity to develop inflammation responses such as granulomas. Concludes that both genetic and environmental factors must be considered when assessing prevention strategies and treatment of interstitial lung disease.

Zhiqiang Q. Siegmann K. Keller A. Matter U. Scherrer L. Siegmann HC.
Nanoparticle air pollution in major cities and its origin.
Atmospheric Environment. Vol. 34(3)(pp 443-451), 2000.
Studied aerosol suspended particles with a diameter below 1mum using 3 detection methods. Applied these methods to examine nanoscale particles found near city motorways, and found the majority were released from diesel engines or faulty catalysts.

4. REPORTS

The following reports were cited by other published articles, but have not been examined. They are included because of their relevance to the topic.

Baron, P. A., Maynard, A. D., and Foley, M. (2002). Evaluation of aerosol release during the handling of unrefined single walled carbon nanotube material. NIOSH Report. NIOSH DART-02–191, December 2002. NTIS PB2003–102401 (cited by Warheit 2004).

Joseph, G. (2002). Industrial hygiene air monitoring report. DuPont Co. internal report, October, 2002 (cited by Warheit 2004).

5. CLINICAL TRIALS

No clinical trials of inhaled nanoparticles were found. Four trials using nanoparticle paclitaxel were identified in the ClinicalTrials.Gov database – searched on 4 August 2005. These are Phase I / Phase II trials currently recruiting patients.

Trial ID	Description	Sponsor
ClinicalTrials.gov Identifier NCT00124943	Trials the use of systemic intracoronary administration of albumin-bound paclitaxel, ABI-007, for the prevention and reduction of restenosis following de novo stenting or following angioplasty for in-stent restenosis.	American Bioscience
ClinicalTrials.gov Identifier NCT00110695	This is a Phase 2, non-randomized study of neoadjuvant treatment with nanoparticle albumin bound paclitaxel (Abraxane) every week for 12 weeks followed by 5-FU, epirubicin, and cyclophosphamide (FEC) every 3 weeks for 4 cycles in women with locally advanced breast cancer.	National Surgical Adjuvant Breast and Bowel Project (NSABP) US
ClinicalTrials.gov Identifier NCT00073723	An open-label, Phase I/II Trial of ABI-007 (cremophor EL-free, protein stabilized nanoparticle paclitaxel) administered weekly in chemotherapy naive patients with advanced non-small cell lung cancer. The mode of administration is not clearly stated.	American Bioscience
ClinicalTrials.gov Identifier NCT00092261	This study will examine and compare the way patients with advanced solid tumor cancers handle two drugs: Taxol and ABI-007. Both drugs contain the active ingredient paclitaxel, but they differ in the inactive components that are needed to allow paclitaxel to be given intravenously.	National Cancer Institute (US)

A current trial of a nanofiltered compound is also listed in ClinicalTrials.Gov. Details are:

Trial ID	Description	Sponsor
ClinicalTrials.gov Identifier NCT00119431	This trial examines the kinetics, efficacy and safety of nanofiltered Cetor (C1-esteraseremmer-N), which is used to treat hereditary angioedema. Part A investigates whether the nanofiltration production method affects the action of the drug in patients with hereditary angioedema.	Sanquin

Two completed trials are listed on the Meta Register of Controlled Trials (searched on 4 August 2005):

Trial ID	Description	Sponsor
ClinicalTrials.gov Identifier NCT00046527	This was an open-label study of ABI-007 and Taxol (a cremophor-free protein stabilized nanoparticle paclitaxel) in patients with metastatic breast cancer.	American Bioscience
ClinicalTrials.gov Identifier NCT00076375	This was a preliminary study of safety and efficacy of topical nanocrystalline silver cream in atopic dermatitis (eczema).	Nucryst Pharma-ceuticals.