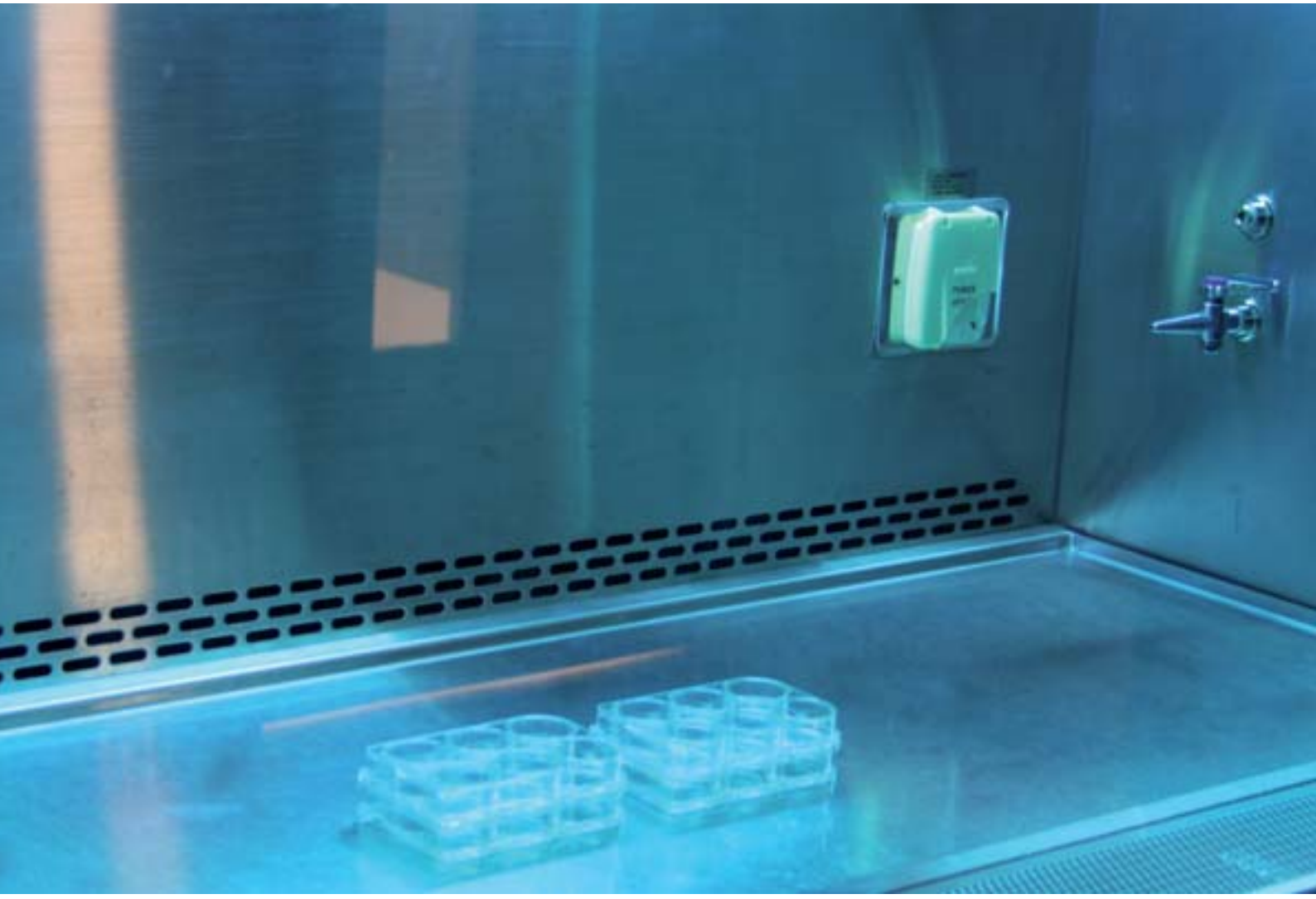
NanoSafe Australia

Current OHS Best Practices for the Australian Nanotechnology Industry

A Position Paper by the **NanoSafe** Australia Network



Plates under UV

Photos provided courtesy of NanoSafe Australia
(Dr Andrew Harford) and Nanotechnology Victoria (Adrian Malec)

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Executive Summary

Advancement of the nanotechnology industry in Australia has seen numerous researchers beginning to handle nanomaterials, as well as the establishment of industrial facilities that are producing nanomaterials for incorporation into consumer products. The introduction of chemicals into Australia is regulated through four federal agencies. After chemicals are assessed and/or registered their use is regulated by state & territory authorities, while Comcare regulates chemical use in Commonwealth facilities. Traditionally, the risk assessment of chemicals relies heavily on the composition of chemicals, and not the physical parameters that are key determinants in the adverse effects caused by nanomaterials such as, size, surface area and surface chemistry. It is now recognised that the unique properties of nanomaterials, which make them attractive materials for use in various products, may result in unique toxicological properties not seen in their bulk states. Workers handling nanomaterials may be exposed to them via inhalation, dermal exposure and ingestion, although workplace levels have not been adequately characterised. Instruments that can monitor the particle number, size distributions and surface areas of nanomaterials in the workplace are available but require a degree of expertise and are relatively expensive. Moreover, workplace exposure standards are currently unavailable and appropriate methods that accurately characterise nanomaterial exposure have not been established. Due to the poorly characterised toxicity of nanomaterials, measures taken to reduce the exposure of workers should apply the "as low as reasonably practicable" (ALARP) approach. This should be achievable through risk management programs that broadly encompass all the hierarchy of risk controls currently used for ultrafine particulates, especially the use of appropriate engineering controls, administrative controls and personal protective equipment.

Foreword

The NanoSafe Australia network is a group of Australian toxicologists and risk assessors, who have formed a research network to address the issues concerning the Environmental Health and Safety (EHS) of nanomaterials. Our mission is to support government, industry and non-government organisations (NGOs) in their efforts to understand the health and safety issues surrounding nanotechnology products and their manufacturing processes, and to provide quality data for the appropriate risk assessments of nanomaterials.

In early 2006, NanoSafe Australia was established following approaches to the Australian Centre for Human Health Risk Assessment (ACHHRA) from Nanotechnology Victoria Pty Ltd. (NanoVic), concerning the need to address EHS and regulatory issues. The network is significant because it represents Australia's first program to deal with the considerable challenges surrounding the EHS of nanomaterials, which requires a co-ordinated approach and collaborations with various specialists in diverse fields of research. Australian toxicologists are experienced in fields of study that are directly related to the issues of nanotoxicology, such as measurement of ultra-fine particles in ambient air, immunotoxicology, toxicokinetics, occupational hygiene and workplace monitoring of toxic agents, ecotoxicology, environmental toxicology and ecological and human health risk assessments. The NanoSafe Australia network is forging partnerships with materials scientists, which will aid toxicology studies by characterising the specific traits of nanomaterials that are important in their bioactivity and toxicity.

Although there are many challenges and gaps in the knowledge concerning the occupational health and safety (OHS) issues surrounding nanotechnologies, this document has been produced for the Australian laboratories and industries that are already handling nanomaterials. This document discusses the OHS best practices using the current, although limited, knowledge. Specifically, it focuses on the health effects of exposure to nanomaterials and methods to reduce exposure. Issues that may arise from increased physical hazards (e.g. explosion and flammability) were considered beyond on the scope of this document, however it should be mentioned that this could be a concern for some newly developed nanomaterials. This document is meant as a general guide for the nanotechnology industries aiming to be proactive in introducing good OHS practices in their workplaces. It is envisaged that it will be reviewed on an annual basis, so that the most recent developments in nanotechnology OHS can be incorporated.

1. Setting the scene

1.1. A short history of nanotechnology

Nanotechnology is a very broad term that crosses into many of the traditional fields of research such as physics, chemistry, electronics, optics, biology and other sub-disciplines within these fields. Exactly when nanotechnology research officially began is somewhat arguable because many colloid researchers, material scientists and biotechnologists have been working with nano-sized materials for decades. Examples include the use for over 50 years of metal oxide nanomaterials in pigments and cosmetics because of their ability to change the viscosity of a solution when shaken or stirred, i.e. their thixotrophic properties (Borm et al., 2006). Nevertheless, there have been some specific milestones that are often identified as the emergence of nanotechnology as a distinct field of research.

In 1959, the prominent American Nobel prize laureate, Richard Feynman, presented his visionary lecture "*There is plenty of room at the bottom*", in which he recognised the potential for manipulating matter on an "atom by atom" basis. Feynman's vision took 27 years to come to fruition and in 1986 the atomic force microscope (AFM) was invented by researchers at IBM. This scanning probe microscope was a significant break-through in nanosciences because it finally gave researchers the tools needed to image, measure and manipulate matter on an atomic basis. The AFM remains one of the foremost tools for

nanotechnology researchers, although alternative scanning probe microscopes have been developed since then. However, the processes needed to manufacture nanomaterials had already begun by this stage and in 1985 a group of researchers at Rice University in Houston, Texas made their Nobel prize-winning discovery of a third structural form of carbon, the C60 fullerene (also known as the "buckyball"). Carbon nanotubes (CNTs) were manufactured and characterised six years later by Sumio Iijima, while he was working for NEC in Japan. The methods he devised have since been modified to produce a number of different forms of CNTs, e.g. singlewalled (SWCNT), multiwalled (MWCNT) and various "chemically doped" versions. Undoubtedly, the field of nanotechnology expanded rapidly in the last decade due to the foresight and support of the US Government administration. In 2000 the formation of the USA's National Nanotechnology Initiative (NNI) was announced, which has invested billions of dollars in the nanotechnology industry over the last 6 years. In 2006, the NNI will distribute approximately 1.2 billion dollars in funding to various government agencies and institutions (NNI (US), 2006).

1.2. The Australian nanotechnology industry

Funding from state and federal government departments has also helped move the Australian nanotechnology industry forward, with funding presently being estimated at $A100 million per annum. The Department of Industry, Tourism and Resources (DITR) reports that 70 groups are working with some aspect of nanotechnology and there are 50 Australian nanotechnology companies, with interests in a diverse range of different disciplines within the nanotechnology field (Invest Australia, 2005). Presently many of the Australian nanotechnology companies, like many of their foreign counterparts, are in the pre-competitive stages of development. Consequently, the personnel presently being exposed to nanomaterials are primarily located in university laboratories and smaller pilot plants. There are currently no reliable data concerning how many people work in the Australian nanotechnology industry. Consumer products containing nanoparticles are already on the market in Australia, e.g. cosmetics and sunscreens that contain zinc oxide (ZnO) and titanium dioxide (TiO2), and there are local industrial facilities supplying nanomaterials for these products. Therefore EHS researchers and regulatory systems already lag behind the present industrial setting and are now attempting to catch up with the rapid developments in nanotechnologies.

At present, the Australian nanotechnology industry is dwarfed by the size of the Australian chemical industry, which employs over 80,000 people and has an annual turnover of approximately $22 billion, i.e. ~1% of the global chemical market (Miller, 2004). However, if the nanotechnology industry grows as predicted, most of the existing chemical industries will be influenced by nanotechnologies and so will be soon producing nanomaterials, or incorporating nanomaterials in their products, or using instruments that contain some form of nanotechnologies. Therefore, the future growth of the multi-billion dollar Australian chemical industry is intimately connected to the development of nanotechnologies.

Recently, the National Nanotechnology Strategy Taskforce (NNST) released their recommendations for the future growth of the Australian nanotechnology industry. The global nanotechnology market has been predicted to be worth $US2.6 trillion in 8 years time and, based on this figure, the Taskforce has estimated that Australian nanotechnology industry could be providing $A50 billion worth of products and services at this time (NNST, 2006).

2. Current regulatory frameworks for the regulation of chemicals in Australia

The introduction of chemicals into Australia is regulated by four federal agencies and the particular agency that is responsible for dealing with a chemical's assessment and registration is based on the designated end-use of the product (Table 1). The Australian Pesticides & Veterinary Medicines Authority (APVMA) is responsible for the registration of agricultural chemicals and veterinary drugs, while the Food Standards Australia New Zealand (FSANZ) regulates additives in food and sets compositional standards, which regulate maximal permitted concentrations of food contaminants. The Therapeutic Goods Administration (TGA) is the agency responsible for the registration of medical devices and products with therapeutic claims. This agency will be involved in the registration of nanomedicines and medical devices at apply nanotechnologies before they can be sold in the Australian market. Furthermore, the TGA is responsible for the regulation of sunscreens, which are already using nanomaterials (e.g. ZnO and TiO2) as protective agents against UV radiation exposure. The National Industrial Chemicals Notification & Assessment Scheme (NICNAS) is the default notification and assessment agency for chemicals not controlled by other legislation. Consequently, their tasks are largely focused on the risk assessment of industrial chemicals. Once chemicals are assessed by NICNAS, they make recommendations to the State and Territory OHS authorities who are responsible for their regulation and use in occupational settings. Comcare is the agency responsible for the regulation of chemicals in Commonwealth facilities. NICNAS assesses new chemicals before they are introduced into Australian industries, while existing or "grandfathered" chemicals, which were in use when NICNAS was established, are assessed on a priority basis. The system for assessing existing chemicals has recently undergone a review, which was aimed to improve NICNAS's efficiency and communication with stakeholders. The recommendations made in this review may see significant changes to the regulation of industrial chemicals in Australia, including the regulation of nanomaterials. The Australian Safety and Compensation Council (ASCC) produces model regulations, codes of practice and set national standards for workplace exposures, which are then adopted by the State and Territory government OHS authorities. The State and Territory authorities are responsible for all chemicals beyond the point of sale, however there are a number of national frameworks, which provide consistent standards between the States, e.g. the Agvet Code; Dangerous Goods legislation; Food Standards Code; National Drugs and Poisons Scheduling (Table 1) (EPHC, 2003).

Table 1. An Overview of Australia chemical regulations schemes†

Introduction of chemicals in Australia*

Chemical Type	Responsible agency	Portfolio	Scope	Relevant legislation
Industrial chemicals	National Industrial Chemicals Notification & Assessment Scheme (NICNAS)	Health and Ageing	Assessment only, not registration based	Industrial Chemicals (Notification and Assessment) Act 1989, as amended 1990
Agricultural and veterinary chemicals	Australian Pesticides & Veterinary Medicines Authority (APVMA)	Agriculture, Fisheries and Forestry	Assessment and product registration	Agricultural and Veterinary Chemicals (Code) Act 1994; Agricultural and Veterinary Chemicals Administration Act 1994
Medicines and medicinal products	Therapeutic Goods Administration (TGA)	Health and Ageing	Assessment and product registration	Therapeutic Goods Act 1989
Food additives, contaminants and natural toxicants	Food Standards Australia New Zealand (FSANZ)	Health and Ageing	Assessment and product registration	Food Standards Australia New Zealand Act 1991; Australia New Zealand Food Standards Code

Following assessment and/or registration

Policy maker	Type of chemical/application	Regulators
FSANZ	Food	FSANZ and State & Territory authorities
ASCC	OHS	State & Territories OHS authorities and Comcare
NICNAS	Prohibited chemicals	Customs
DEH[1]	Environment	State EPA[8], Territory authorities and Comcare
TGA	Therapeutics	TGA and State & Territory health authorities
DAFF[2]	Agricultural and veterinary chemicals	APVMA, State & Territory authorities and Comcare
OCS[3]/ACCC[4]	Consumer chemicals and products	State & Territory authorities and Comcare
DOTARS[5]/NTC[6]	Dangerous Goods transport	State & Territory authorities
PM&C[7]/DOTARS[5]	Security sensitive chemicals	State & Territory authorities and Comcare

† Further details can be found in EPHC, 2003. * modified from http://www.nicnas.gov.au/Chemicals_In_Australia/Chemical_ Schemes.asp.[1] Dept. of Environment and Heritage,[2] Dept. of Agriculture, Fisheries and Forestry,[3] Office of Chemical Safety,[4] Australian Competition and Consumer Commission,[5] Dept. of Transport and Regional Services,[6] National Transport Commission,[7] Dept. of the Prime Minister and Cabinet, [8] Environment Protection Authorities/Agencies.

The present regulatory processes rely heavily on the composition of the chemicals. However, it is now recognised that this basis has a crucial gap in chemical regulation when dealing with nanomaterials. For example, carbon fullerenes and nanotubes are currently regulated on the same basis as graphite because they are all pure forms of carbon, yet they differ significantly in their properties. This serious gap is common to the regulatory frameworks of every country, nevertheless some governments (e.g. USA) are attempting to use their existing frameworks to regulate nanotechnologies. In Australia, the federal policy makers are currently researching the issues of nanotechnology regulation and whether the existing regulatory frameworks are sufficient. It could be possible to set exposure standards based on size-fractions, particle number or surface area, however there is currently a lack of health effect information, which is needed to inform detail within the frameworks. It should be noted that silica and asbestos have exposure standards based on size-fraction and particle number and were developed under the existing regulatory frameworks (NOHSC, 1995). Australian agencies are co-operating with the international efforts to harmonise the regulation of nanotechnologies, including the regulatory harmonisation and nanotechnology projects of the Organisation for Economic Co-operation and Development (OECD), and the World Health Organisation's (WHO) International Program for Chemical Safety (IPCS). Additionally, the ASCC is the lead agency for the introduction of the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) into Australia.

Although there may be gaps in Australian regulatory systems, the experiences of related industries have made the nanotechnology industry acutely aware that there is no such thing as a "lawless" product, and that other legislative principles still apply. Even if nanotechnologies are not specifically regulated, legislation concerning the duty of care and specific product liabilities are issues the industry can not ignore. For example, tobacco and asbestos products were developed at a time of limited specific regulation, but this did not prevent the manufacturers of these products from becoming targets of liability suits due to adverse health effects caused by these products. These examples highlight the need for proactive regulation and consequently the nanotechnology industries have been calling for the clarification of regulatory frameworks so that they can proceed in a more certain regulatory environment (van Calster, 2006).

3. Issues surrounding nanomaterial exposure

3.1 Toxicity

This paper will only briefly discuss the toxicity of nanomaterials, as there have been numerous seminal reports and review articles detailing the scientific evidence that nanomaterials have unique toxicological properties and are more toxic than their bulk materials (RS/RAE, 2004, Oberdorster et al., 2005, Borm et al., 2006, IRSST, 2006, NIOSH, 2006, HSE (UK), 2004, ASCC, 2006). When considering nanomaterial toxicity it is extremely important to recognise that there are many different types of nanomaterials - negating a generic approach. Indeed, studies in both tissue cultures and laboratory animals have shown that seemingly slight changes to the surface chemistry of nanomaterials can result in significant changes in their toxicity. For example, fullerenes and CNTs that were chemically treated in different ways (i.e. "functionalised") showed remarkably different toxicities compared to their untreated counterparts (Carrero-Sanchez et al., 2006, Sayes et al., 2004). Consequently, the detailed characterisation of nanomaterial properties is now recognised as a critical component of quality nanotoxicology studies. Furthermore, it seems unlikely that future studies will provide generalisations that can describe the toxicity of all nanomaterials (Borm et al., 2006). This means that the nanotechnology regulators in Australia will probably need to introduce further classifications for nanomaterials based on their size/surface area, surface chemistry and composition. Undoubtedly, the classification systems that are eventually chosen will be based on the globally-standardised systems that are currently being devised through the nanotechnologies projects of the OECD and International Standards Organisation (ISO).

The number of nanotoxicology studies being conducted is gradually increasing but there are many knowledge gaps that need to be filled before appropriate risk assessments and workplace exposure standards can be established. Data concerning the effects of engineered nanomaterials in humans are limited and to date the majority of studies have been conducted in rodent models and tissue cultures using tumour cell lines. Nevertheless, the studies conducted thus far have identified a number of fundamental issues concerning the toxicity of nanomaterials. The most common finding is that the particle size, surface area and surface chemistry are all key determinants in the adverse effects caused by particulate matter. Secondly, one of the most reported adverse effects is that inhalational exposure to high levels of nanomaterials results in inflammation and damage to the lungs.

The exact cause of nanomaterial-induced inflammation has not yet been clarified, although a number of hypotheses have emerged. [1]The most prominent hypothesis is that the cellular damage may be due to the ability of some nanomaterials to produce reactive oxygen species (ROS), which can damage cell membranes and proteins (Xia *et al.*, 2006). [2]Nanomaterials have the ability to adsorb many different environmental contaminants to their surfaces due to their large surface areas and chemical natures. [3]Nanomaterial-induced toxicity and inflammation could be due to chemical "contaminants" that are adsorbed to the surface of nanomaterials (e.g. bacteria-derived molecules, catalyst metals or combustion waste-products from manufacturing processes). Additionally, chemicals attached to nanomaterials may be presented to receptors on the surface of immune cells, which could result in inflammation (Vallhov *et al*., 2006, Becker *et al*., 2005). Alternatively, toxic chemicals adsorbed to particles, such as metals and combustion waste products, may also be delivered into cells resulting in toxic effects (Penn *et al*., 2005). Some environmental research groups are using the theoretical term "nanovectors", which reflects this characteristic of nanomaterials as a portal of entry for cellular uptake of toxic moieties.

Overall, these findings suggest that the mechanism of toxic action of nanomaterials may depend on the processes used to produce engineered nanomaterials and the materials' ability to adsorb chemicals to their surfaces. It is therefore possible that some processes used in quality fabrication of nanomaterials, such as using dust-free clean rooms and sterile cabinets, could also reduce the toxicity of nanomaterials - however this is yet to be proved. Presently, there is evidence for all hypotheses but future research will demonstrate whether the mechanisms are operating independently, synergistically, or if one mechanism is more damaging than the other.

The structure and strength of CNTs is worthy of special mention because it has raised concerns with toxicologists due to their structural similarities with asbestos. Although no information is available concerning the health effects of CNTs in human subjects, they have been unflatteringly labelled "the new asbestos" in some publications. This is because in animal models they both appear to cause lung disease (e.g. fibrosis) by "frustrating" the immune system, causing it to over-react which results in lung damage. This over-reaction occurs because the immune system is not equipped to eliminate these very strong fibres and cells that attempt to engulf CNTs appear to be harmed by them (i.e. frustrated phagocytosis), causing suppression of their cellular functions (Jia *et al*., 2005).

Additionally, immune cells that cannot consume the CNTs because they are too long, will remain attached to them and become activated to produce chemical messengers (i.e. cytokines), which attract more frustrated immune cells, resulting in more damage to the surrounding healthy tissue. Consequently, occupational hygienists have made statements such as "…*For the moment, it would be no bad thing if they [CNTs] were to be treated by those making and using them as though they were asbestos*…" (Seaton, 2006). However, it should be noted that most of the CNT experiments to date have observed acute diseases states only with high concentrations of CNTs instilled into the respiratory system of rodents (Warheit *et al*., 2004, Shvedova *et al*., 2005, Carrero-Sanchez *et al*., 2006, Muller *et al*., 2005). It is unlikely that these concentrations of CNTs would be inhaled in real-life situations or that such high levels will be present in workplaces. These studies indicate one possible mechanism of CNT toxicity, but investigation of chronic exposure to low concentrations are yet to be conducted and will provide more realistic data, with a greater value to the risk assessment process.

3.2 Routes of exposure

Due to the extremely small size of nanomaterials, there is a concern that they can access the body through routes that would not be possible for their larger counterparts. It was initially assumed that nanomaterials were so small that they would not be deposited in the lungs and upon entering the body they would be rapidly eliminated. The limited amount of evidence collected to date has shown that these assumptions are untrue and toxicologists are now quantifying the bioavailability of nanomaterials through various routes of exposure.

3.2.1. Inhalation

Inhalation is the route of exposure receiving the greatest amount of attention because it is the most likely to occur in nanotechnology occupational settings. Furthermore, an extensive body of data already exists concerning the human health effects of inhaled urban air "ultrafine particles" (UFPs), as well as toxic occupational aerosols, such as asbestos and silica. Although the study of engineered nanoparticles is still in its infancy, data from these related studies have provided sufficient evidence to suggest that nanomaterials can penetrate deep into the lungs, resulting in adverse effects, not only in the lungs, but also at secondary sites such as the cardiovascular (heart and blood vessels) system. The location where nanomaterials are deposited within the respiratory system depends on a number of parameters, including particle size, external air speed, orientation to the prevailing air movement direction, and the volume of air inhaled (Martonen *et al*., 2005).

Extensive modelling of inhaled radionucleotide deposition in the respiratory system was conducted in the early 1990s by the International Commission on Radiological Protection (ICRP, 1994) and this model is now being used to predict the deposition of inhaled nanomaterials in the respiratory tract. The model predicts that particles of approximately 5-20 nm in size have the greatest ability to travel deep into the lungs, while extremely small (i.e. <5 nm) and larger particles (i.e. > 100 nm) will be deposited in the nose and throat region. However, the application of this model is made increasingly difficult because it does not predict the behaviour of nanomaterial aggregates, which will probably exist in most nanotechnology workplaces. Furthermore, the size distributions of aerosolised nanomaterials are dynamic – changing through coagulation, aggregation and agglomeration. The coagulation rate of an airborne nanomaterial depends on the concentration of particles in the air – at high concentrations it is significant but at low concentrations it is negligible (Maynard and Kuempel, 2005). Nevertheless, aggregating nanoparticles increase in size in both gas and liquid phases, which results in a subsequent decrease in particle number concentration and overall surface area (Won Lee and Kwon, 2006). Due to the fundamental importance of these properties to nanomaterial toxicity and bioavailability, progressive particle aggregation would probably reduce toxicity and bioavailability over a period of time. However, nanomaterial aggregates may also disaggregate, especially if their environmental conditions change when moving between biological or environmental compartments. Disaggregation is not well studied but such an effect may increase the bioavailability and toxicity of nanomaterials. Consequently, Lee and Kwon (2006) stated that, "…*in many basic and applied fields… the evolution of the particle size distribution because of coagulation is of fundamental importance and interest*…", and this is especially true for the field of nanotoxicology. The measurement of particle concentration and their changing size distribution in "real-time" is currently a major challenge and there are also relatively few reports of worksite monitoring in nanotechnology facilities. Nevertheless, particle size is fundamentally important in determining nanomaterial toxicity. Therefore this paper supports the recent call for the real-time air monitoring of nanotechnology workplaces in Australia (ASCC, 2006). Instruments that are capable of real-time air monitoring of airborne nanomaterials are available on the Australian market, see Table 2.

Protecting workers from the inhalation of nanomaterials should be the primary focus of nanotechnology facilities. Fortunately, some of the processes that are presently being used to produce nanomaterials are conducted in closed areas, which will also provide workers with protection against exposure. For example, the electronics industry handle their nanoparticles in "clean rooms" that exist to protect the delicate components they are producing, however these processes will also reduce the exposure of workers (Seaton, 2006). In comparison to predictions for the future, nanomaterial production is currently low and nanomaterials are of high value, which means that worker exposure may be limited at this time. However, as production increases and the value of materials decrease, there will probably be an increased exposure to workers. This situation is well recognised by the industry, government and academic institutions, and is a major reason why a proactive approach has been called for by many NGOs (RS/RAE, 2004).

3.2.2. Olfactory bulb and the brain

The olfactory bulb is a mass of nerve cells located between the nose and the brain and is connected to both via a short chain of nerve cells. The absorption of nanoparticles into the brain via olfactory bulb was first demonstrated in 1941 with polio virus particles (Bodian and Howe, 1941). Since then it has also been demonstrated with metal and metal oxide nanoparticles (de Lorenzo, 1970, Elder *et al*., 2006), as well as carbon-based UFPs (Oberdorster *et al*., 2004, Oberdorster *et al*., 2005). The data in this field of research are currently limited and require further strengthening before their significance can be fully appreciated. Nevertheless, due to the potentially serious consequences of neurotoxicity in the central nervous system, these studies further emphasize the need for protection against the inhalation of nanomaterials in the workplace. Measures taken to prevent inhalation, especially through the nose, will also aid in reducing worker exposure to possible neurotoxic effects.

3.2.3. Dermal

A limited number of studies have investigated the ability of nanomaterials to penetrate through the dead layers of the skin (the stratum corneum) and into the living skin tissue (the dermis), where damage and further distribution may occur. ZnO and TiO_2 have been studied to some degree because of their use in sunscreens and cosmetics, but also because there were concerns that they might damage skin cells *in situ* via photoactivity when exposed to UV light. However, it has been recognised that damage occurs only if the particles are absorbed through the skin. Sunscreens are extremely important for Australian public health, prompting the Therapeutic Goods Administration (TGA) to conduct a review of the available scientific literature. They recently concluded that "*…initial studies are limited in number and have proved inconclusive…*". However this did not prevent the TGA from stating that "*…the weight of current evidence* [i.e. two studies] *is that they remain on the surface of the skin and in the outer dead layer (stratum corneum) of the skin…*" (TGA, 2006).

Dermal penetration studies have been conducted with quantum dots (QD), which are semiconducting nanocrystals that consist of a colloidal core, usually containing metals such as cadmium and selenium, surrounded by one or more surface coatings, e.g. zinc sulfide. QD exist in various shapes (i.e. spherical and ellipsoid) and possess various surface chemistries (i.e. positive, negative and neutral charges). Of the six different types of QD studied, only the negatively charged ellipsoid QD were unable to penetrate the skin after 8 h (Ryman-Rasmussen *et al*., 2006a). Further experiments using cultured skin cells have shown that QD may also get inside the skin cells, but their ability to cause inflammation depended on surface chemistry, with negatively charged QDs being most potent (Ryman-Rasmussen *et al*., 2006b). These data indicate that the shape and surface charge of particles will influence the ability of nanomaterials to penetrate the skin and cause adverse effects. Furthermore, all precautions should be used to prevent the skin coming in contact with QDs.

There are many questions yet to be answered regarding the absorption of nanomaterials through the skin. Most nanomaterials have not been sufficiently assessed for their ability to penetrate intact skin and there have been no investigations concerning the effect of skin condition on the rate of absorption, e.g. broken skin and dermatitis.

3.2.4. Ingestion

The oral ingestion of nanomaterials in the workplace may occur after the accidental swallowing of nanomaterials, but can also occur following inhalation because some nanomaterials will be transported by normal mucociliary elimination processes to the throat to be swallowed (Maynard and Kuempel, 2005). The issue of exposure by ingestion appears to be of low priority to toxicologists and there are only a few specific studies concerning the absorption of nanomaterials through the gastrointestinal tract (GIT). Although many more studies will need to be conducted, ingestion has been described as "*…a more benign exposure route…*" (ASCC, 2006), because the GIT consists of a thick protective mucosal barrier and acidic environment. Studies that have investigated the fate of fullerenes after they have been ingested, reported that most (98%) were not absorbed by the GIT and were eliminated in the faeces. However, 2% of the fullerenes were eliminated in the urine indicating that at least some uptake from the GIT had occurred (Yamago *et al*., 1995). Other nanoparticles, specifically TiO_2 (Jani *et al*., 1994) and polystyrene nanoparticles (Jani *et al*., 1990), can also be absorbed from the GIT of laboratory animals, however their bioavailability was also low (about 10%). Variations in surface chemistry are thought to be responsible for variation in nanomaterial uptake, however particle size is once again a key factor. The study that used different-sized polystyrene beads found that smaller particles are absorbed more readily than larger particles (Jani *et al*., 1990).

Many more studies are required to determine the significance of oral ingestion in the toxicity of nanomaterials. It is unknown what effect the varying acidic and alkaline environments of the GIT have on large aggregates and functionalised nanomaterials that enter the system. For example, the GIT environment may break down aggregates into smaller particles, while the surface chemistry nanomaterials may be altered by the GIT environment. Changing the size and surface chemistry of nanomaterials will undoubtedly alter their bioavailability in the GIT and this needs to be investigated.

3.2.5. Systemic translocation

Systemic translocation refers to the ability of nanomaterials to enter the blood stream and travel to sites distant from the area of absorption, which can result in adverse effects at secondary organs, especially the liver, kidneys, heart, blood and immune system. As mentioned above, there is evidence in the literature, which suggests that UFPs can move from the lungs into the blood stream and thereby reach other organs (Oberdorster *et al*., 2002, Nemmar *et al*., 2002). Some nanomaterials (e.g. QDs) can penetrate through the skin and would be expected to enter the blood stream via dermal capillaries, although it has not yet

been shown. Additionally, the bioavailable fraction of swallowed TiO_2 and polystyrene particles travels via the portal blood stream to the liver and spleen. The TiO_2 nanoparticles were also distributed to other organs, such as the lung and peritoneal tissues, while the polystyrene nanoparticles were found in the bone marrow (Jani *et al*., 1990, 1994). Overall, these findings suggest that the adverse effects of nanomaterials may not be localised and secondary sites of damage should be investigated. Unfortunately, investigations of the tissue distribution and physical state of nanomaterials in intact animals is hampered by the significant challenges of detecting nanomaterials and their existing particulate state once they are in a complex biological system.

3.2.6. Metabolism, elimination and bioaccumulation

The elimination pathways for most nanoparticles are yet to be determined, but there are concerns that they may be retained within certain organs and bioaccumulated. Poorly-metabolised synthetic chemicals that bioaccumulate (e.g. persistent organic pollutants, POPs) are of specific interest to toxicologists because continued exposure to these chemicals can result in remarkably high tissue levels (referred to as the "body burden"). Not only do cells appear to lack the ability to metabolise nanomaterials, but the problem may be compounded by the inhibition of crucial enzymes that detoxify other chemicals, i.e. cytochrome P450 enzyme inhibition by some nanomaterials, specifically fullerenes (Ueng *et al*., 1997). Studies concerning the bioaccumulation of nanomaterials have not yet been reported and require significant time and resources. However, it is well-recognised that chronic low-dose studies are more relevant to human health risk assessments and these experiments are on-going at this time. If nanomaterials are shown to bioaccumulate, this will add an additional risk factor to their use and also their disposal in the environment. Furthermore, environmental chemists and ecotoxicologists also need to investigate whether nanomaterials biomagnify in the environment, i.e. increase in concentration moving up the food chain, like POPs.

4. Monitoring of ambient nanomaterial exposure

4.1. Measurement of toxic agents in the workplace

The measurement of target chemicals in the air has a twofold role; first in estimating the likely (or relative) dose in those exposed to that environment, and second, to allow a comparison with some standard, guideline or other benchmark indicating compliance at an exposure level considered to be of low (or at least acceptably low) risk. While the process of risk assessment based on dose is the domain of the toxicologist, occupational hygienists are the professionals who specialise in the measurement of workplace hazards. The Australian Institute of Occupational Hygienists (AIOH) can provide details of Certified Occupational Hygienists who may be able to provide valuable assistance in this regard (www.aioh.org.au).

The main issue for the toxicologist in estimating dose is the use of the appropriate metric or unit of measurement that relates to toxic effects. Traditionally, the measurement of airborne toxic chemicals in occupational settings has been through the use of instruments that measure a mass of toxic agent per volume of air, e.g. mg/m^3 or ppm. Additionally, the regulation of airborne toxic agents is through the use of exposure limits expressed in the same terms. Instruments that measure chemicals on a mass per volume basis are available for use within the nanotechnology industry, however there is strong agreement within the scientific community that this is not an appropriate measurement for nanoparticle exposure and that size distribution and surface area/chemistry are more significant. Furthermore, the sensitivity of many devices is insufficient when measuring the low particle masses that are typical in nanotechnology industrial operations. Additionally, the normal background of particles in an indoor environment can be several thousand nanoparticles per millilitre, resulting in extremely "noisy" measurements (Seaton, 2006). Ideally, pro-active industries that conduct workplace monitoring of airborne nanomaterials should measure a range of parameters by a number of different methods, e.g. size distribution and surface area. The instrumentation presently used to fully characterise nanomaterials requires a large amount of expertise (e.g. electron microscopy), and are labour intensive and expensive. Therefore, it is unlikely that the nascent nanotechnology industry will begin to monitor their workplaces without the cooperation of government and academic institutions with suitable funding support for research. Small Australian companies involved in nanotechnology manufacture are in particular need of assistance because these companies do not have the resources to employ specialist advisors.

Specialised nanomaterial monitoring instruments are available and have been used for many years to measure UFPs and toxic dusts in workplaces. Currently, some instruments are expensive and the cost is directly related to the size of particle being measured, the extent of information provided and the counting rate (Table 2). For example, Condensation Particle Counters (CPC) have the benefit of being small and portable, and can report airborne particle number concentrations but are not size-selective and are still relatively expensive, i.e. ($A7,500-$A60,000). They may be useful as initial warning systems for detecting problems, and are most useful at worksites where the other characteristics of the nanomaterials are familiar and consistent, and where they have been calibrated against more sophisticated instruments. Scanning mobility particle sizers (SMPS) have been used extensively in industry for many years because they are able to provide information concerning the size distribution of airborne particles. Diffusion charges have the ability to provide information concerning the surface area of particles and newer instruments have been developed to estimate the surface area of particles deposited in the lungs, e.g. the Aerotrak 9000. A detailed discussion of the specific advantages and disadvantages associated with the use of the instruments described in Table 2 are beyond the scope of this

Table 2: Instruments for the monitoring of nanotechnology workplaces

Instrument	Capabilities/Limitations	Models	Price ($A)	Manufacturers
Mass based aerosol monitors *Note: Mass-based measurements have limited applicability in the nanotechnology industry. Still used by a number of industries to measure larger airborne particulates to comply with workplace exposure standards (WES).	Real-time mass measurements of aerosols 100nm – 10µm. May not be applicable to nanotechnologies but 3000 units are used in Australia for compliance of traditional industry WES.	DustTrak	6,400	TSI Inc., USA[a]
Personal Aerosol Monitors *Worn by worker	Real-time ***mass*** measurements of aerosols 100nm – 10ìm for personal exposure estimations.	AM510	5,000-5,200	TSI Inc., USA[a]
Condensation Particle Counters (CPC) * Older models required butanol but water-based models are now sold by TSI Inc.	Counts all particles in aerosols but not size specific. Some measure down to 5 nm. Some products are hand-held (HH) and battery operated. Other models can provide counts in real-time.	P-Trak (HH) (20nm-1000nm) TSI 3007-4 (HH) (10nm-1000nm) Other models (many available)	7,500 15,000 19,000 - 60,000	TSI Inc., USA[a] TSI Inc., USA[a] GRIMM, Germany[b] Dekati, Finland[c]
Electrical Low Pressure Impactor (ELPI)	Provides particles size distributions and concentration in real-time. Sensitive to 7nm with accessories. Now superseded by other models due to resolution limitations.	Only one model sold by Dekati	160,000 (including accessories for 7nm particles)	Dekati, Finland[c]
Scanning Mobility Particle Sizers (SMPS)	Counts particles with a CPC or FCE after they have been separated into numerous size channels by DMAs. Can provide results in real-time.	Many models sold by TSI & GRIMM	70,000 – 150,000 77,000 – 330,000	TSI Inc., USA[a] GRIMM, Germany[b]
Fast Mobility Particle Sizer (FMPS) Engine Exhaust Particle Spectrophotometers (EEPS) Fast Automotive Particle Emission Spectrometer (FAPES)	Combines a number of DMA and FCE units for extra sensitivity of size measurements. Provides real-time information and fast counting abilities. Some models specifically designed to measure car particulate emissions for compliance with regulations.	FMPS EEPS 3090 FAPES	123,000 133,000 330,000	TSI Inc., USA[a] TSI Inc., USA[a] GRIMM, Germany[b]
Nanoparticle ***Surface Area*** Monitors * New Instruments developed by TSI, aiming to specifically address toxicity issues	New specialised instruments that indicate the surface area of particles that deposit in the lung (using the ICRP models). Sensitive to 10 nm. Real-time ***surface area*** and concentration measurements.	AEROTRAK™ 9000 TSI - 3550	19,000 27,000	TSI Inc., USA[a] TSI Inc., USA[a]

[a] http://www.tsi.com/Category.aspx?Cid=111 The Australian agent for TSI Inc. is Kenelec Scientific, www.kenelec.com.au ;
[b] http://www.grimm-aerosol.com/html/en/nanoparticle-dust-monitors.htm; c http://www.dekati.com/2-1.shtml.
The Australian agent for GRIMM and Dekati is Ecotech, www.ecotech.com.au

paper, but specialised occupational hygiene assistance should be sought when embarking upon a monitoring program.

4.2. Studies on aerosol formation

The ability of nanoparticles to aerosolise is important because it will significantly influence the air concentration of nanomaterials in workplaces. Aerosols will be produced during the production of nanomaterials in gas phases, however these processes are usually confined and only leaking equipment would result in exposure to workers. Of greater significance is the formation of aerosols during maintenance of production systems and handling of dry nanopowders (Maynard and Kuempel, 2005). Fortunately, studies to date show that some nanomaterials do not readily aerosolise and the rapid coagulation of nanoparticles indicates that the concentration of nanomaterial in workplace may be reduced. Nevertheless, the production of nanoparticle aerosols will be influenced by many factors and the dynamics are not yet well understood. It is an area of active research and current studies are focusing on developing testing protocols to determine the release of inhalable and respirable particles from nanopowders (Maynard and Kuempel, 2005). The assessment of industrial processes and materials handling methods that may lead to the release of nanomaterials should be performed by professionally competent occupational hygienists.

However, some observations appear to suggest that the risk of aerosol release may not be high. For example, laboratory and field studies conducted by NIOSH have reported that SWCNTs were not easily aerosolised and therefore the air concentrations when handling them were low. However, fumed alumina that was used as a reference in the study was more readily aerosolised and emitted air concentrations 100 times higher that CNTs (Maynard *et al*., 2004). A study investigating the air concentrations of fine and ultrafine particles in a bagging room of a carbon black manufacturing operation found that air concentrations were 20 times higher than background measurements, but the majority of these particles were larger that 400 nm (Kuhlbusch *et al*., 2004). Once nanoparticles are in the air they behave like gases (e.g. they follow air flows and do not readily settle), which means workers should be protected from exposure through the use of traditional control methods (Maynard and Kuempel, 2005), see next section.

5. The use of engineering controls and personal protective equipment (PPE)

The capability of engineering controls and personal protective equipment (PPE) to protect nanotechnology workers is an area of intense interest and a current focus of researchers. Although exposure control methods have not been well-characterised for nanomaterials, the limited experimental data and theoretical considerations indicate that conventional ventilation, engineering and filtration controls should be effective and therefore applied in all nanotechnology workplaces (Maynard and Kuempel, 2005). High-Efficiency Particulate Air (HEPA) filters have been in use since the 1950s and are found in air-purifying respirators, specialised vacuum cleaners, biohazard cabinets and some fume-hoods. They are used in many different industries (e.g. biomedical and automotive industries), where they have already been protecting workers from nano-sized particulates, e.g. viruses and combustion particulates. The ability of HEPA filters to remove nanomaterials from the air is currently under investigation but a strong history of research suggests that these filters will remove engineered nanomaterials through the processes of impaction and diffusion (Hinds, 1999).

5.1. Fume-hoods and biological safety cabinets

Nanomaterial aerosols are highly mobile and have gas-like dynamics, therefore ventilation systems such as fume-hoods and biological safety cabinets with HEPA filters should be effective in removing aerosols of nanomaterials from the workplace and environmental emissions (NIOSH, 2006). Of course, class III biological safety cabinets will offer workers the highest level of protection but such a level of protection is probably not required and class II is considered sufficient. Laminar flow cabinets are not recommended because they blow potentially contaminated air from the sample towards the operator, leading to a higher risk of exposure. Fume-hoods and cabinets should be certified by the National Association of Testing Authorities (NATA) and their efficiency should be tested at least annually. Details of appropriate ventilation system design, specifications and maintenance can be found in the seminal guidelines published by the American Conference of Government Industrial Hygienists (ACGIH, 2001).

5.2. Protective clothing and gloves

Protective clothing, including gloves and footwear, is used extensively in many different industries and it serves to protect the worker from dermal exposure to contaminants. The effectiveness of protective clothing to reduce exposure to nanomaterials is currently being investigated by NIOSH and results will be made available on their website (NIOSH, 2006). As stated earlier, there are still many uncertainties concerning the absorption of nanomaterials through the skin. Therefore workers should wear protective clothing that covers all areas of the skin and protective footwear (e.g. disposable shoe covers or neoprene shoes) may also be considered. Change rooms and laundry services should also be provided to workers, so that workers do not take clothing contaminated with nanomaterials to their home.

The use of protective clothing will limit the dermal exposure of workers, however it has been reported that the efficiency of clothing for macro-scale powders is low (Schneider et al., 2000, NIOSH, 2006). Therefore, if OHS managers believe that dermal exposure may be significant for the nanomaterials they are producing (e.g. QDs), they could also consider additional dermal protection through the use of Tyvek® or polypropylene overalls, over the top of fabric overalls. Additionally, it is not yet

known to what extent gloves are an effective barrier against nanomaterials, nor which glove material affords most protection. For example, nitrile and polypropylene polymer gloves have a smaller pore size and may provide greater protection than latex gloves. It is recommended at this time that two pairs of gloves should be worn, with extra protection from gloves made from different materials (e.g. nitrile or polypropylene over the top of latex). Furthermore, continued flexing of the gloves during use can lead to cracks and holes that nanomaterials could penetrate (Schwerin *et al*., 2002), therefore disposable gloves should be changed on a regular basis throughout the day.

5.3. Respirators

Air-purifying respirators protect workers by removing harmful dusts, fumes, chemical vapours and gases by filtering the contaminated air through either a fibrous membrane or resin. They have been used for many decades by a diverse range of industries and their effectiveness has been well researched. Past studies have given researchers confidence that respirators provide adequate protection against silica dust, urban air and combustion particulates. However, it is necessary to note that respirators should only be used as a last resort if other engineering controls are not available. In addition, respirators are also only effective if they are properly fitted and workers need to be trained in their use (HSE (UK), 2004). The respirators used in nanotechnology facilities should comply to the Australian standard AS/NZS 1716:2003 (Respiratory protective equipment) and more information concerning the use and choice of respirators for a specific workplace can be found in the Australian Standard AS/NZS 1715 (Selection, use and maintenance of respiratory protective devices), which discuss protection against particulate matter.

The current advice being provided to the nanotechnology industry by occupational hygiene experts is that certified HEPA-respirators will be effective in protecting workers from nanomaterials, e.g. P100 and N100 respirators are expected to remove at least 99.9% of particles. NIOSH have stated that, "*Preliminary evidence shows that for respirator filtration media there is no deviation from the classical single-fiber theory for particulates as small as 2.5 nm in diameter*" (NIOSH, 2006). It is believed that nanoparticles are removed from the air by diffusing onto the filtering fibres of the respirator, while large particles (i.e. >300nm) will be physically blocked by the filter fibres (Hinds, 1999). Presently, respirators are only certified for use with particles that are 300 nm in size because they have the lowest probability of being captured and efficiencies are believe to be greater with particles smaller and bigger than this size. Nevertheless, their performance for nanomaterials is currently being studied and results should be released in the very near future (NIOSH, 2006).

6. Clean-up and disposal of nanomaterials

The maintenance and cleaning of nanotechnology facilities during normal operations or after an accidental spill represents scenarios where worker exposure could be significantly increased. It is recommended that facilities are cleaned using only HEPA filter vacuum cleaners that comply with the Australian standards AS 3544-1988 (Industrial vacuum cleaners for particulates hazardous to health) and AS 4260-1997 (High Efficiency Particulate Air Filters (HEPA) – Classification, Construction and Performance). Household vacuum cleaners should never be used even if the have a HEPA filter installed in them. Alternatively, nanotechnology workplaces could be cleaned using wet-wiping methods but whichever method is chosen, it should be conducted in a manner that limits the inhalational and dermal exposure of workers.

The fate of nanomaterials released into environment is not yet known. Preliminary environmental chemistry data indicates that some nanomaterials are likely to form large agglomerates in the environment and/or bind tightly to the soil, which will reduce their bioavailability and movement between environmental compartments. However, due to the current uncertainties, precautions should be taken when disposing of nanomaterials at this time. The disposal of some metal and metal oxide nanomaterials (i.e. QDs and ZnO) is currently restricted by the Australian State and Territory authorities because they are potent biocides (ASCC, 2006). However, there are currently no guidelines for the disposal of many nanomaterials (e.g. fullerenes and CNTs) but efforts should be taken to contain them and presently they should be handled as hazardous waste. At the very least, nanomaterials should be double-bagged, enclosed in rigid impermeable container and disposed of in a licensed land-fill site. Binding the nanomaterials within some matrix (e.g. concrete) would provide additional protection from their release into the environment. These procedures should be achievable at this time because the volume of nanomaterials being disposed of is low due to their high value.

7. Potential implications of poor practices

A disturbing legacy has been left behind by some industries that have produced toxic dusts during, and as a by-product of, their processes. The lives of many thousands of Australian workers have been affected and legal claims as a result of exposure to toxic dusts involve billions of dollars (Australian Senate, 2006). This history has resulted in mistrust of employers by industrial workers and their families, and has made many investors and companies nervous about the future of the nanotechnology industry and their substantial investments in the industry. Nevertheless, it is these hard-learned lessons that should prevent such events from occurring again and there are a number of reasons why this is less likely to be the fate of the nanotechnology industry.

Firstly, many beneficial and simple OHS practices have been introduced into Australian workplaces over the last few decades and most of these will also protect the health of nanotechnology workers. Secondly, there is now a stronger legislative framework for the protection of workers and there are avenues for unsatisfied workers to seek redress if they feel unsafe in their workplaces.

Thirdly, the nanotechnology industry is being proactive, as it has the unique opportunity to predict what issues they will meet in the future and are able to take early steps to reduce the health risk to their workers. Finally, the processes used to produce nanomaterials are vastly different from some of the past activities (such as open-cut mining of asbestos), which led to the past exposure of workers to high-levels of toxic dusts. While poor practices within the nanotechnology industry may lead to the exposure of workers, it appears highly unlikely in the current workplace environment that the nanotechnology industry will result in an epidemic of harm to workers.

8. Conclusions

There are many gaps in the knowledge still to be filled before appropriate risk assessments and workplace exposure standards can be established. Therefore, the authors of this position paper support the recommendations of the report commissioned for the ASCC (2006), which states that "*The generally accepted approach is the application of a hierarchy of risk controls which incorporate the broad elements of elimination, substitution, engineering controls, administrative controls and – finally – the use of personal protective equipment*".

Specifically, until appropriate workplace exposure standards can be established, the nanotechnology industry should control exposures through the application of risk management programs using the "*As Low As Reasonably Practicable*" (ALARP) approach. Substitution is unlikely to be an applicable hazard reduction method because the unique properties of nanomaterials will drive their production and use. Nevertheless, traditional engineering and administrative controls and the use of PPE will be effective in reducing the exposure of workers, therefore these should be used in all nanotechnology facilities.

Finally, NanoSafe Australia believes that although there many uncertainties concerning the health effects of nanomaterials, this should not prevent the industry from moving forward because there are numerous measures that can be taken, which will limit the exposure of nanotechnology workers and minimise the harm that nanotechnologies cause to Australian workers. Continued monitoring of current and emerging exposure and health relationships will permit early identification of unforeseen risks and the adoption of measures to mitigate them.

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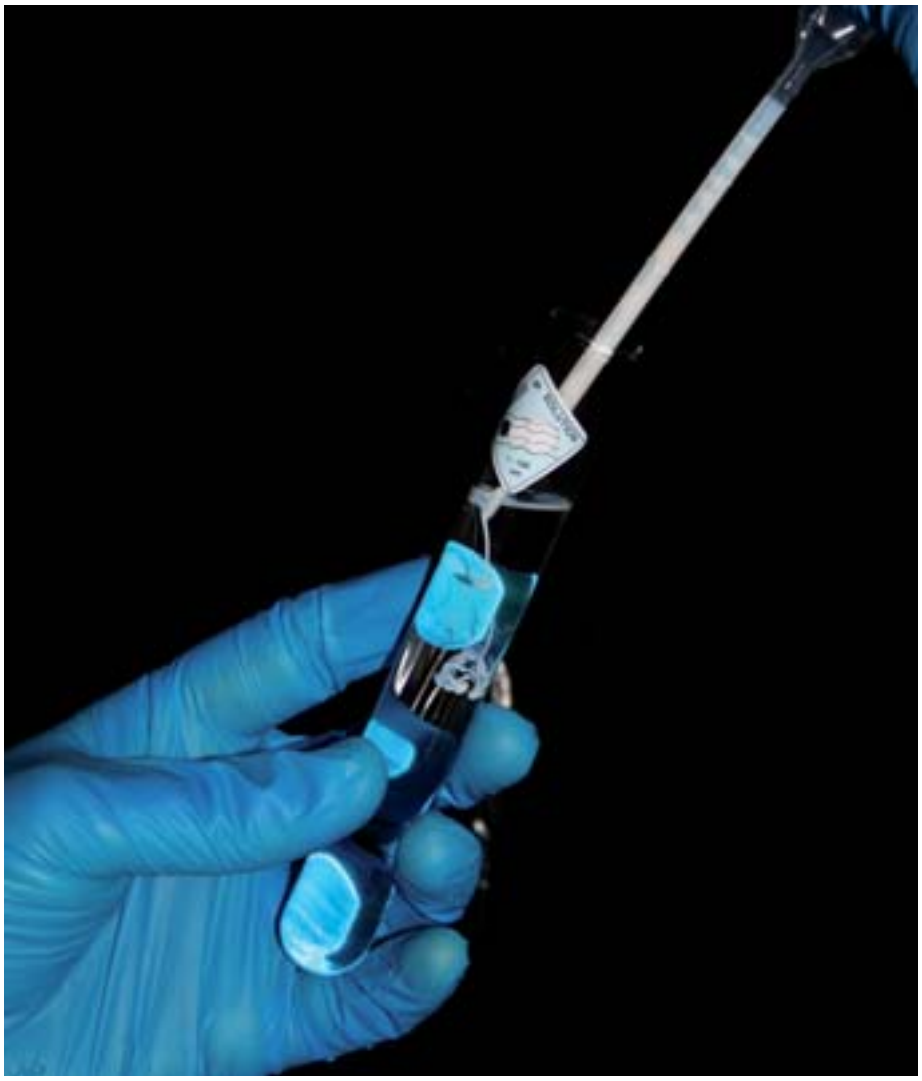

Mixing ZnO in Water

Applying Sunscreen

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