ISSN:1991-8178

**Australian Journal of Basic and Applied Sciences**

Journal home page: www.ajbasweb.com

# Toxicity, Occupational Exposure Risks and Management Framework for Nanomaterials used in Singapore

Kavitha Palaniappan

*University of Newcastle Singapore, Division of Environmental and Occupational Health and Safety, Faculty of Health and Medicine, Singapore*

**ARTICLE INFO**

***Article history:***
*Received 12 March 2015*
*Accepted 28 April 2015*
*Available online 6 June 2015*

***Keywords:***
*Nanotechnology, Nanotoxicology, Occupational Exposure*

**ABSTRACT**

Nanotechnology plays a key role in the technological revolution of this century. Singapore outranks the world as an investment destination and advancements in the field of nanotechnology is becoming a significant contributor to its growth. Currently there are a handful of companies and research organizations that are involved in the development, manufacturing and commercialization of nanomaterial products and applications in Singapore. However, very little research focuses on the toxicological aspects and occupational exposure of the nanomaterials that are being used. Moreover, the toxicological aspects that are studied mainly include in vitro testing, animal studies and cellular toxicities. It is important to note that in vitro studies may not take into account the translocation, toxico-kinetics and coordinated tissue responses towards the nanoparticles that are most likely to happen in vivo. Human exposure to nanomaterials and their effects are yet to be looked at and with the alarming differences in toxicity of nanomaterials compared to their non-nano counterparts, this angle of research comes as a necessity in the current scenario. This paper provides a summary of the toxicities of the nanomaterials that are being used in Singapore, namely, nano-titanium dioxide, nano-silver, nano-carbon, nano-cerium oxide, nano-calcium carbonate, nano-zinc oxide and nano-silicon carbide followed by a theoretical framework to determine the occupational exposure risks to nanomaterials in Singapore and possible management practices that could be employed to overcome this adverse situation.



**To Cite This Article:** Kavitha Palaniappan, Toxicity, Occupational Exposure Risks and Management Framework for Nanomaterials used in Singapore. ***Aust. J. Basic & Appl. Sci.,*** *9(22): 8-17, 2015*

## INTRODUCTION

The US-based research institute Business Environment Research Institute (BERI), in its BERI Report 2014-I (April 2014) has ranked Singapore first for cities with the best investment potential ("RANKINGS"). Singapore, with a land area of 700 sq.km ("Land area (sq. km) in Singapore") and a population of 5.47 million in June 2014 ("Welcome to Statistics Singapore") has been showing a constant growth in its GDP and has proved to be a prosperous market-based economy. Several multinational companies use Singapore as a springboard into Asia to seek potential partners and gain quick access to the global market. Singapore relies heavily on its intellectual property and also has a conducive environment for enterprises to start up and thrive.

More than a quarter of Singapore's economy is contributed by its manufacturing sector and its clusters are always on the lookout for new sources of innovation and technology to enhance their competitive edge. Given its extensiveness across all industries, nanotechnology will be a critical area for development to enhance the performance of existing products as well as to create new products and processes. In recent years, worldwide investment in nanotechnology research and development has seen a drastic rise and Singapore has also recognized the importance of nanotechnology. It is actively promoting the development of nanotechnology and is aspiring to become one of the leading players in this ground. Singapore has several organizations and networks that are committed to promote and explore nanotechnology. It efficiently links the intellectual capital, research expertise and the market space in order to enable the new products and applications to be created, market tested and commercially exploited.

### *Nanotechnology r&d and commercial organizations:*

The Nanoscience and Nanotechnology Cluster of Singapore is a network of research centers in Singapore that are involved in nanofabrication, nanocharacterization and exploitation of nanotechnology applications. The Institute of

**Corresponding Author:** Kavitha Palaniappan, University of Newcastle, Division of Environmental and Occupational Health and Safety

Bioengineering and Nanotechnology promotes interdisciplinary research and works on nanofabricated devices. The Institute of Materials Research and Engineering concentrates on nanoimprinting. The National University of Singapore has set up a Nanoscience and Nanotechnology Initiative to promote nanotechnology research and also has several labs that work on nanotechnology: Nano Biomechanics Lab, Nanocore and Silicon Nano Device Laboratory. The outstanding developments in the field of nanotechnology by these R&D organizations range from multi-axis nanopositioning systems for high end machines, silica coated stirrer bars made up of iron oxide nanoparticles, thin film nano-silicon solar cells to new improved anti-reflective plastics.

Moving over to commercial organizations in Singapore, it is imperative to realize that nanotechnology is such a diverse field that it spans over several industries linking up many different applications and products. Nanomaterials Technology Pte Ltd (NMT) specializes in development, manufacturing, commercialization and licensing of nanomaterial products for various markets such as oil and gas, coatings, plastics, glass, electronic materials, pharmaceutical and specialty chemicals ("NanoMaterials Technology"). This company uses the High Gravity Controlled Precipitation (HGCP) technology to synthesize nanoparticles. nanoYo manufactures and distributes a nano-sized titanium dioxide (TiO2) semiconductor photocatalyst. Huper Optik develops and manufactures nano-ceramic coatings, whereas Omniyo manufactures nanocoatings and Nanofilm Technologies International has shown remarakable advancement in thin film deposition through its Filtered Cathodic Vacuum Arc (FCVA) coating technology ("Nanofilm Technologies International Pte Ltd"). V-Kool manufactures nanoscale coatings for glass surfaces and Qtech Nanosystems has expertise in nanodynamics technology.

Quantum Precision Instruments develops atomic precision sub-nanometer and sub-nanoradian positioning metrological devices and Nano Electro-Mechanical Systems (NEMS) ("Quantum Precision Instruments – Products"). There are also semiconductor industries like Chartered Semiconductor Manufacturing and WinTech Nano-Technology Services that work with nanomaterials. Curiox Biosystems has enabled miniaturization of heterogeneous bioassay for researchers through nanotechnology and Inspiraz Technology has come up with antiviral, antimicrobial and hydrophobic coatings based on silver, carbon and photocatalyst nanoparticles ("Inspiraz"). Helios Applied Systems works on 3D nanofabrication enabling the manufacture of arbitrary 3D polymer structures that has sub-micron resolution. Energenics has also come up with alternative energy solutions through nanotechnology. Apart from these industries that work directly with nanomaterials, there are also nanotech consulting companies like NanoConsulting and NanoGlobe which drive the nanotech businesses towards sustainable development.

***Nanotoxicology for sustainable nanotechnology:***

As seen all this while, nanotechnology is a vast developing field with applications ranging over a wide arena of industries. However, it is alarming to note that the growth of nanotechnology is surpassing the research activities related to potential health hazards of nanoparticles that are being used. In general, nanoparticles are basically defined as materials with at least one dimension in the nanoscale (100 nanometers or smaller) (Paik *et al*., 2008). Further, recent literature suggests that the small size of the particles may contribute to a different range of toxic effects and some nano forms may have unique toxicological properties compared to their non-nano forms; for example, carbon nanotubes may cause mesothelioma-like pathology in human tissue whereas the other carbon particles do not cause such a reaction (Heinemann and Schafer, 2009). Likewise, NIOSH has established a different recommended exposure limit (REL) for nano-titanium dioxide due to its unique toxicity characteristics (Zalk *et al*., 2009).

Nanotoxicology deals with the study of toxicity of nanomaterials and is mainly used to determine whether and to what extent the new and unique properties of nanomaterials may pose a threat to the environment and to human health (Buzea *et al*., 2007). There are several factors that contribute to the unique toxicity of these materials and the major factors that have been studied include size, particle surface area and chemistry (Suh *et al*., 2009), crystallinity, coating and the longevity of the particles (Schlesinger, 1995). Several studies have demonstrated that certain nanomaterials cause toxicity in biological systems like oxidative stress in inflammatory and immunological systems and pre-inflammatory cytotoxin activity in the lungs, liver, heart and brain (Hussain *et al*., 2009). Some nanoparticles are also associated to genotoxicity, carcinogenicity and teratogenicity (Medina *et al*., 2009).

Moving on to the local context of Singapore, the major nanomaterials used in the industrial as well as R&D organizations include nano-titanium dioxide, nano-silver and nano-carbon (mainly for nanocoatings), nano-crystalline chrome nitride for ceramic coatings and nanoparticulate cerium oxide as diesel fuel additives. NMT uses a wide range of nanomaterials like nano precipitate calcium carbonate, nano-zinc oxide dispersion, nano-cerium oxide dispersion, nano-antimony tin oxide dispersion and nano-silicon carbide ("NanoMaterials Technology"). Several studies have been done pertaining to the toxicity of most of these nanomaterials. However, studies need to be done

when it comes to certain nanomaterials like nano-crystalline chrome nitride and nano-antimony tin oxide. A brief outline of the established toxicities of these nanomaterials that are widely used in Singapore is given below.

***Nano-titanium dioxide toxicity:***

Several studies have shown that titanium dioxide nanoparticles are capable of inducing inflammatory responses and Reactive Oxygen Species (ROS) in a wide variety of cell types and tissues [(Gurr *et al*., 2005), (Grassian *et al*., 2007), (Long *et al*., 2006), (Renwick *et al*., 2004), (Warheit *et al*., 2006)]. Nano-titanium dioxide is said to reach epidermis and sometimes even the dermis, through the human stratum corneum (Lademann *et al*., 1999). Sayes *et al*., (2006) and Braydich-Stolle *et al*., (2009) reported that nano-titanium dioxide either induced cell necrosis or initiated apoptosis by the formation of ROS in mouse keratinocyte cell line HEL-30.

Titanium dioxide nanoparticles are also known for increasing the lymph-node burdens and causing inflammation (C. L. Tran, D. Buchanan, R. T. Cull, 2000). Another study reported that nano-titanium dioxide particles were also capable of reducing the ability of macrophages to phagocytose other particles (Renwick *et al*., 2001).

Wang & Fan, (2014) have stated that nano-titanium dioxide can deposit in the alveolar region and access the lung interstitium after inhalation exposure, eliciting a pulmonary inflammatory response and lung injury and that the factors that play an important role in this toxicity include size, crystal phase, dispersion and agglomeration status, surface coating and chemical composition.Park *et al*., (2008) have reported cell death, ROS increase, reduced glutathione (GSH) decrease and induction of oxidative stress-related genes such heme oxygenase-1, thioredoxin reductase, glutathione-S-transferase, catalase and hypoxia-inducible gene when human bronchial epithelial cell line BEAS-2B was exposed to different concentrations (5, 10, 20 and 40 μg/mL) of nano-titanium dioxide.

Titanium dioxide nanoparticles were also shown to impair the cell's ability to repair DNA, thereby confirming their genotoxic potential (Jugan *et al*., 2012). Titanium dioxide nanoparticles are sometimes found to translocate to systemic organs from the respiratory and gastro-intestinal tracts; however, a recent study states that there is still an enormous lack of epidemiological data regarding the toxicity of nano-titanium dioxide (Shi *et al*., 2013).

***Nano-silver toxicity:***

Nano-silver is said to cause concentration-dependent reduction in cell viability; silver nanoparticles had cytotoxic effects on human liver HepG2 cell line and primary liver cells of mice (Faedmaleki *et al*., 2014). Trop *et al*., (2006) have also reported impaired liver function due to exposure to silver nanoparticles. Takenaka *et al*., (2001) and Sung *et al*., (2008) have shown that the lungs and liver are the major target tissues for prolonged exposure to silver nanoparticles. Inhalation exposure studies done by Oberdörster *et al*., (2004) and Elder *et al*., (2006) indicate that the lung may be the easy target organ for silver nanoparticles and that inhaled particles may deposit in the olfactory mucosa of the nasopharyngeal region and subsequently may get translocated into the brain through the olfactory nerve. In another study, occurrence of systemic argyria after ingestion of nano-silver clearly indicates that it has translocated from the gastro-intestinal tract (Chung *et al*., 2010). Further, it was also demonstrated that silver nanoparticles reduced the cell viability of alveolar macrophages and lung epithelial cells (Soto *et al*., 2007). Silver nanoparticles were also found to be toxic to keratinocytes (Paddle-Ledinek *et al*., 2006) and fibroblasts (Poon and Burd, 2004).

Nano-silver is also said to have certain effects on the human reproductive system: it can cause toxicity to germ line stem cells by reducing the mitochondrial function and inducing membrane leakage and apoptosis (Braydich-Stolle, 2005). Further, when tested in zebrafish, nano-silver demonstrated dose-dependent toxicity in embryos and was also found distributed in brain, heart, yold and blood of embryos (Asharani *et al*., 2008). In rats, nano-silver showed dose-dependent effect on alkaline phosphatase and cholesterol and there was twofold accumulation of silver nanoparticles in kidneys of female than male (Kim *et al*., 2008). Thus, there is some evidence that nano-silver is toxic to a variety of tissues including lung, liver, brain, skin and reproductive organs.

***Nano-carbon toxicity:***

In vitro studies have shown that carbon nanoparticles are capable of stimulating human platelet aggregation and accelerating the rate of vascular thrombosis in rat carotid arteries (Radomski *et al*., 2005). To demonstrate the importance of surface area to volume ratio, ultrafine nano-carbon black particles with 270 $m^2/g$ surface area was found to cause greater pulmonary toxicity in rats compared to larger sized carbon black particles with 22 $m^2/g$ surface area (Nikula *et al*., 1995). Further, it was found that nano-carbon played a significant role in the pathogenesis of rat lung tumors by causing inflammation and epithelial hyperplasia that led to mutations and genotoxic effects (Driscoll *et al*., 1996). For the first time, workplace exposure of nano-carbon black particles and their effects were evaluated in a group of eighty one nano-carbon black exposed workers and the authors suggested that nano-carbon black could be responsible for lung function reduction and the secretion of pro-inflammatory cytokines in the exposed workers (Zhang *et al*., 2014). In the same study, they have also reported thickening of alveolar wall and accumulation of large amounts of inflammatory cells

in lung tissues of mice exposed to nano-carbon black aerosol.

Cytotoxic effects of carbon nanotubes were demonstrated by Barillet *et al*., (2010) and it was stated that the cytotoxicity neither depended on the length nor the purity of the carbon nanotubes. Carbon nanotubes were found to cause cell injury by the process of membrane damage and this was also cell line-dependent. Lam *et al*., (2006) reported that carbon nanotubes were capable of producing inflammation, epithelioid granulomas, fibrosis and biochemical changes in the lungs of rodents. They have also indicated that fine nano-carbon is capable of inducing cardiopulmonary diseases. In the same study, it was also demonstrated that single-walled carbon nanotubes can also produce respiratory function impairments, damage mitochondrial DNA in aorta, induce atherosclerotic lesions in the brachiocephalic artery of the heart and also slow down bacterial clearance. Further, Renwick, Donaldson, & Clouter, (2001) reported that carbon nanoparticles significantly reduced the ability of the macrophages to phagocytose other particles.

***Nano-cerium oxide toxicity:***

Park, Choi, Park, & Park, (2008) evaluated different sizes of nano-cerium oxide in the range of 15, 25, 30 and 45 nm and found that they caused toxicity, ROS increase, GSH decrease and also induced oxidative stress-related genes such as heme oxygenase-1, catalase, glutathione-S-transferase and thiorexoxin reductase in cultured human lung epithelial cells BEAS-2B. The toxicity was actually through the apoptotic process by triggering the activation of cytosolic Caspase 3 and chromatic condensation due to the increase in ROS. Lin *et al*., (2006) subjected human broncho-alveolar carcinoma derived cell line to cerium oxide nanoparticles and found that the toxicity correlated to both dose and exposure time. They also reported generation of free radicals that caused oxidative stress. Yet another study has also reported about the oxidative stress and cytotoxicity of cerium oxide nanoparticles (Karakoti *et al*., 2010).

***Nano-calcium carbonate toxicity:***

Soluble nano-calcium carbonate was found to cause morphological changes in the cell and also inhibited colony formation (Horie *et al*., 2014). In the same study, it was also found that exposure to nano-calcium carbonate caused the release of intracellular calcium, thereby disrupting the effect of calcium signaling. It was highlighted that calcium carbonate nanoparticles may have the potential to influence cellular events if inhaled.

***Nano-zinc oxide toxicity:***

Generally, nano-zinc oxide particles have shown to demonstrate greater in vitro toxicity compared to many other nanoparticles [(Wang *et al*., 2006), (Lanone *et al*., 2009)]. When evaluating the relative toxicity of $TiO_2$, ZnO, $Fe_3O_4$, $Al_2O_3$ and $CrO_3$ nanoparticles in the size range of 30 to 45 nm and concentrations up to 200 µg/mL on Neuro-2A cells, ZnO was found to be highly toxic (Jeng and Swanson, 2006). Yang *et al*., (2009) showed that compared to other nanoparticles, zinc oxide nanoparticles exerted more cytotoxic effects which are attributed to its particle composition and more oxidative stress which is attributed to the particle shape in mouse embryo fibroblast.

Looking at more specific effects, zinc oxide nanoparticles were shown to cause toxic effects on mouse neural stem cells and those effects were dose-dependent but not size-dependent (Xiaoyong Deng *et al*., 2009). Huang *et al*., (2010) studied the effects of nano-zinc oxide in human bronchial epithelial cells. They reported that the cytotoxicity of zinc oxide nanomaterials were both time and concentration dependent and the exposure also led to oxidative stress, membrane damage and an increase in intracellular calcium levels. While studying the gene expression, the authors have mentioned that zinc oxide nanoparticles were capable of altering the transcriptional regulation in the bronchial epithelial cells by increasing the expression of four genes that are involved in apoptosis and oxidative stress responses. Zinc oxide nanoparticles were also noted to damage DNA in sperm cells and lymphocytes (Gopalan *et al*., 2009).

It was found that total protein levels, metallothionein mRNA and lung pathology increased with increasing inhalation exposure of nano-zinc oxide in mice (Wesselkamper *et al*., 2001). After gastro-intestinal administration of zinc oxide nanoparticle suspension in mice, Wang *et al*., (2008) identified liver, spleen, heart, pancreas and bone as the target organs for the zinc oxide nanoparticles. Hidaka *et al*., (2006) reported that zinc oxide nanoparticles that were extracted from commercial sunscreens were highly photoactive and caused rapid DNA damage under in vitro conditions.

Following its high toxicity, some human exposure studies have also been done pertaining to nano-zinc oxide (Beckett *et al*., 2005). Inhalation exposure of human subjects to air containing 0, 2.5 and 5 mg/m3 nano-zinc oxide for 2 hours on separate days revealed metal fume fever symptoms and an elevation of plasma levels of IL-6 (Fine *et al*., 2000). In another study, inhalation exposure of human subjects to air containing an average of 33 mg/m3 for 10-30 minutes resulted in an elevation of biomarkers for pulmonary inflammation (Kuschner *et al*., 1997).

***Nano-silicon carbide toxicity:***

Generally, nano-silicon carbide is considered biologically inert ((Bruch *et al*., 1993a) (Bruch *et al*., 1993b)) as it does not cause harmful effects on tissues. However, in vivo exposure to silicon carbide nanoparticles have shown to cause lung

inflammation (Cullen and Miller, 1997), bronchoalveolar hyperplasia, severe lung fibrotic changes (Akiyama *et al*., 2007) and granulomas (Vaughan *et al*., 1993). In vitro toxicity studies of silicon carbide nanoparticles showed remarkable pro-oxidative reactions and inflammatory responses based on their surface area, crystallite size, crystallite phase, surface oxidation and iron impurities (Pourchez *et al*., 2012). However, they did not show any cytotoxicity.

Svensson *et al*., (1997) have mentioned that in vitro exposure to nano-silicon carbide led to the generation of ROS. S. Barillet *et al*., (2010) stated that in vitro exposure to silicon carbide nanoparticles caused an accumulation in A549 lung epithelial cells which is a major cell redox status disturbance and can also lead to DNA damage. Another study reported that silicon carbide nanoparticles caused cell injury through mitochondrial activity impairment (Sabrina Barillet *et al*., 2010). Silicon carbide nanocrystals possess photoluminescence properties and are presumed to be highly biocompatible, especially to blood and hence are used as biological labels for cell imaging applications (Fan *et al*., 2008). The other side of this application is that they are capable of distributing themselves in the entire cell, thereby potentially interacting with DNA and consequently leading to cytotoxicity and/or genotoxicity. Such toxicological effects still remain in the gray side and are yet to be studied.

***Occupational exposure of nanoparticles:***

Comprehensive studies related to the toxicity of most of the nanoparticles used is currently available in literature; however, rates of workplace exposure, either accidental or otherwise, during the process of manufacturing, processing, storing, transporting or through commercial products is yet to be established. As even a very small quantity of nanoparticulate material can contain huge amounts of individual nanoparticles, low level chronic exposure through inhalation or ingestion or skin or eyes is very much possible in the workplace. Apart from the routes of exposure, there are several other factors that need to be considered when we look into workplace exposure: emission sources, combustion processes, air flow dynamics, ventilation rate, worker mobility (Brouwer *et al*., 2004). The other variables pertaining to the nanoparticles themselves, include: particle size, particle mobility, agglomeration patterns and nature (Maynard and Kuempel, 2005). The various workplace variables that may influence the potential for exposure to nanoparticles is depicted in figure 1.

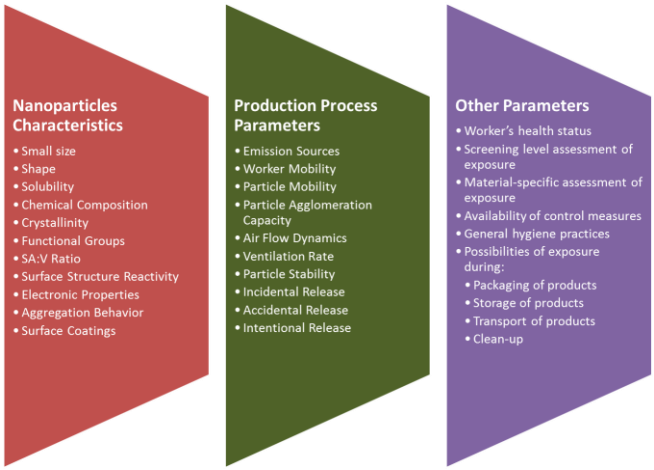


**Fig. 1:** Workplace variables that may influence the potential for exposure to nanoparticles

***Exposure assessment and risk management of nanoparticles:***

Very few studies pertaining to workplace exposure to nanomaterials have been done so far. In one study, laboratory and field measurements on the exposure of workers to single-walled nanotubes was performed (Maynard *et al*., 2004). In another study, Methner *et al*., (2007) tried to identify the potential sources of workers' exposure to carbon nanofibers during polymer composite laboratory operations. In their study, Schneider and Nordic Council of Ministers, (2007) summarized the sources of exposure from engineered nanoparticles as drilling and cutting operations of carbon nanotube-doped concrete and cleaning operations in the laboratories. However, with increasing production and use of nanomaterials, it is necessary to have more information so as to recognize, evaluate and avoid risks pertaining to these materials.

The main aspects of exposure assessment should include:

1 Identification of nanomaterials;
2 Description of exposure;
3 Possibilities of accidental or incidental exposure;
4 Nanomaterial-specific toxicity assessment:
a. Modes of entry of the nanomaterials;
b. Potential for translocation of the nanoparticle to other parts of the body;

c. Toxico-kinetics of the nanomaterial;
d. Clearance mechanisms of the nanomaterial from the body.

5 Measurement of exposures to nanomaterials (Methner *et al*., 2009):

a. Identification of possible sources of emission;
b. Estimating particle number concentration sampling to locate areas of suspected release;
c. Proper sampling at suspected release points;
d. Concentration mapping using continuous direct reading measurements so as to understand changes over time and space (Ramachandran *et al*., 2011).

6 Risk Assessment for the nanomaterials;
7 Availability and efficacy of protective measures if any;
8 Practical handling guidelines for activities involving nanomaterials;
9 Conducting awareness and training for workers involved in use of nanomaterials.

When it comes to occupational health surveillance of workers being potentially exposed to nanoparticles, Nasterlack *et al*., (2008) express that there is no evidence-based foundation for a "nano-specific" occupational medical screening and that one can only perform general medical screening with methods targeted at some of the health outcomes which have been highlighted to be occurring due to exposure to nanomaterials.

Traditionally, risk management would be based on comparison of an exposure to existing standards of allowable limits. However, when it comes to occupational exposure limits for nanomaterials, currently there aren't any enforceable regulations for most of the nanomaterials. In this scenario, the application of risk management techniques is totally based on professional judgment. There are two schools of approaches: reduce the exposure to "as low as reasonably practicable" (ALARP) and control banding approach, wherein uncertain nanomaterials are placed in high-risk bands that require more stringent control measures. Whatever the strategy be, the first priority is to protect the workers by implementing appropriate primary preventive measures and to begin with, the basic risk management strategy which is the hierarchy of control: elimination or substitution, isolation, engineering controls, administrative controls and personal protective equipment can be practiced by all organizations that work with nanomaterials.

***Conclusion:***

The rapid development of nanotechnology can be maintained in a sustainable manner along with research activities pertaining to nanotoxicology at workplace level in order to safeguard the health and well-being of workers and also to familiarize the occupational safety and health professionals with the available strategies for understanding the exposure parameters and managing the risks through effective control measures that can be put in place. This paper has summarized the various types of nanomaterials that are being widely used in the industrial and research and development sectors of Singapore, their associated toxicities, health hazards and their potential for human exposure, followed by possible exposure and risk assessment and management framework for such nanomaterials. It is also vital to note that there is a significant need for further research in this field of occupational exposure to nanomaterials in Singapore.

## REFERENCES

Akiyama, I., A. Ogami, T. Oyabu, H. Yamato, Y. Morimoto, I. Tanaka, 2007. Pulmonary Effects and Biopersistence of Deposited Silicon Carbide Whisker After 1-Year Inhalation in Rats. Inhal. Toxicol, 19: 141–147. doi:10.1080/08958370601051784

Asharani, P.V., Y. Lian Wu, Z. Gong, S. Valiyaveettil, 2008. Toxicity of silver nanoparticles in zebrafish models. Nanotechnology 19, 255102. doi:10.1088/0957-4484/19/25/255102

Barillet, S., A. Simon-Deckers, N. Herlin-Boime, M. Mayne-L'Hermite, C. Reynaud, D. Cassio, B. Gouget, M. Carrière, 2010. Toxicological consequences of TiO2, SiC nanoparticles and multi-walled carbon nanotubes exposure in several mammalian cell types: an in vitro study. J. Nanoparticle Res. 12, 61–73. doi:10.1007/s11051-009-9694-y

Barillet, S., M.L. Jugan, M. Laye, Y. Leconte, N. Herlin-Boime, C. Reynaud, M. Carrière, 2010. In vitro evaluation of SiC nanoparticles impact on A549 pulmonary cells: Cyto-, genotoxicity and oxidative stress. Toxicol. Lett. 198, 324–330. doi:10.1016/j.toxlet.2010.07.009

Beckett, W.S., D.F. Chalupa, A. Pauly-Brown, D.M. Speers, J.C. Stewart, M.W. Frampton, M.J. Utell, L.S. Huang, C. Cox, W. Zareba, G. Oberdörster, 2005. Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults: a human inhalation study. Am. J. Respir. Crit. Care Med., 171: 1129–1135. doi:10.1164/rccm.200406-837OC

Braydich-Stolle, L., 2005. In Vitro Cytotoxicity of Nanoparticles in Mammalian Germline Stem Cells. Toxicol. Sci. 88, 412–419. doi:10.1093/toxsci/kfi256

Braydich-Stolle, L.K., N.M. Schaeublin, R.C. Murdock, J. Jiang, P. Biswas, J.J. Schlager, S.M. Hussain, 2009. Crystal structure mediates mode of cell death in TiO2 nanotoxicity. J. Nanoparticle Res., 11: 1361–1374. doi:10.1007/s11051-008-9523-8

Brouwer, D.H., J.H.J. Gijsbers, M.W.M. Lurvink, 2004. Personal exposure to ultrafine particles in the workplace: exploring sampling techniques and strategies. Ann. Occup. Hyg, 48: 439–453. doi:10.1093/annhyg/meh040

Bruch, J., B. Rehn, H. Song, E. Gono, W. Malkusch, 1993a. Toxicological investigations on silicon carbide. 1. Inhalation studies. Br. J. Ind. Med., 50: 797–806.

Bruch, J., B. Rehn, W. Song, E. Gono, W. Malkusch, 1993b. Toxicological investigations on silicon carbide. 2. In vitro cell tests and long term injection tests. Br. J. Ind. Med., 50: 807–813.

Buzea, C., I.I. Pacheco, K. Robbie, 2007. Nanomaterials and nanoparticles: Sources and toxicity. Biointerphases 2, MR17. doi:10.1116/1.2815690

Chung, I.S., M.Y. Lee, D.H. Shin, H.R. Jung, 2010. Three systemic argyria cases after ingestion of colloidal silver solution. Int. J. Dermatol, 49: 1175–1177. doi:10.1111/j.1365-4632.2009.04380.x

Cullen, R.T., B.G. Miller, 1997. Short-term inhalation and in vitro tests as predictors of... Environ. Health Perspect. Suppl, pp: 105-1235.

Driscoll, K.E., J.M. Carter, B.W. Howard, D.G. Hassenbein, W. Pepelko, R.B. Baggs, G. Oberdörster, 1996. Pulmonary inflammatory, chemokine, and mutagenic responses in rats after subchronic inhalation of carbon black. Toxicol. Appl. Pharmacol, 136: 372–380. doi:10.1006/taap.1996.0045

Elder, A., R. Gelein, V. Silva, T. Feikert, L. Opanashuk, J. Carter, R. Potter, A. Maynard, Y. Ito, J. Finkelstein, G. Oberdörster, 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ. Health Perspect, 114: 1172–1178.

Faedmaleki, F.H., F. Shirazi, A.A. Salarian, H. Ahmadi Ashtiani, H. Rastegar, 2014. Toxicity Effect of Silver Nanoparticles on Mice Liver Primary Cell Culture and HepG2 Cell Line. Iran. J. Pharm. Res. IJPR, 13: 235–242.

Fan, J., H. Li, J. Jiang, L.K.Y. So, Y.W. Lam, P.K. Chu, 2008. 3C-SiC Nanocrystals as Fluorescent Biological Labels. Small, 4: 1058–1062. doi:10.1002/smll.200800080

Fine, J.M., T. Gordon, L.C. Chen, P. Kinney, G. Falcone, J. Sparer, W.S. Beckett, 2000. Characterization of clinical tolerance to inhaled zinc oxide in naive subjects and sheet metal workers. J. Occup. Environ. Med. Am. Coll. Occup. Environ. Med., 42: 1085–1091.

Gopalan, R.C., I.F. Osman, A. Amani, M. De Matas, D. Anderson, 2009. The effect of zinc oxide and titanium dioxide nanoparticles in the Comet assay with UVA photoactivation of human sperm and lymphocytes. Nanotoxicology, 3: 33–39. doi:10.1080/17435390802596456

Grassian, V.H., P.T. O'shaughnessy, A. Adamcakova-Dodd, J.M. Pettibone, P.S. Thorne, 2007. Inhalation exposure study of titanium dioxide nanoparticles with a primary particle size of 2 to 5 nm. Environ. Health Perspect, 115: 397–402. doi:10.1289/ehp.9469

Gurr, J.R., A.S.S. Wang, C.H. Chen, K.Y. Jan, 2005. Ultrafine titanium dioxide particles in the absence of photoactivation can induce oxidative damage to human bronchial epithelial cells. Toxicology, 213: 66–73. doi:10.1016/j.tox.2005.05.007

Heinemann, M., H. Schafer, 2009. Guidance for handling and use of nanomaterials at the workplace. Hum. Exp. Toxicol, 28: 407–411. doi:10.1177/0960327109105149

Hidaka, H., H. Kobayashi, T. Koike, T. Sato, N. Serpone, 2006. DNA Damage Photoinduced by Cosmetic Pigments and Sunscreen Agents under Solar Exposure and Artificial UV Illumination. J. Oleo Sci., 55: 249–261. doi:10.5650/jos.55.249

Horie, M., K. Nishio, H. Kato, S. Endoh, K. Fujita, A. Nakamura, S. Kinugasa, Y. Hagihara, Y. Yoshida, H. Iwahashi, 2014. Evaluation of cellular influences caused by calcium carbonate nanoparticles. Chem. Biol. Interact, 210: 64–76. doi:10.1016/j.cbi.2013.12.013

Huang, C.C., R.S. Aronstam, D.R. Chen, Y.W. Huang, 2010. Oxidative stress, calcium homeostasis, and altered gene expression in human lung epithelial cells exposed to ZnO nanoparticles. Toxicol. In Vitro, 24: 45–55. doi:10.1016/j.tiv.2009.09.007

Hussain, S., S. Boland, A. Baeza-Squiban, R. Hamel, L.C.J. Thomassen, J.A. Martens, M.A. Billon-Galland, J. Fleury-Feith, F. Moisan, J.C. Pairon, F. Marano, 2009. Oxidative stress and proinflammatory effects of carbon black and titanium dioxide nanoparticles: Role of particle surface area and internalized amount. Toxicology, 260: 142–149. doi:10.1016/j.tox.2009.04.001

Inspiraz [WWW Document], n.d. URL http://www.inspiraz.com.sg/ (accessed 4.7.15).

Jeng, H.A., J. Swanson, 2006. Toxicity of metal oxide nanoparticles in mammalian cells. J. Environ. Sci. Health Part A Tox. Hazard. Subst. Environ. Eng., 41: 2699–2711. doi:10.1080/10934520600966177

Jugan, M.L., S. Barillet, A. Simon-Deckers, N. Herlin-Boime, S. Sauvaigo, T. Douki, M. Carriere, 2012. Titanium dioxide nanoparticles exhibit genotoxicity and impair DNA repair activity in A549 cells. Nanotoxicology, 6: 501–513. doi:10.3109/17435390.2011.587903

Karakoti, A., S. Singh, J.M. Dowding, S. Seal, W.T. Self, 2010. Redox-active radical scavenging nanomaterials. Chem. Soc. Rev., 39: 4422. doi:10.1039/b919677n

Kim, Y.S., J.S. Kim, H.S. Cho, D.S. Rha, J.M. Kim, J.D. Park, B.S. Choi, R. Lim, H.K. Chang, Y.H. Chung, I.H. Kwon, J. Jeong, B.S. Han, I.J. Yu, 2008. Twenty-eight-day oral toxicity, genotoxicity, and gender-related tissue distribution of silver nanoparticles in Sprague-Dawley rats. Inhal. Toxicol, 20: 575–583. doi:10.1080/08958370701874663

Kuschner, W.G., A. D'Alessandro, H. Wong, P.D. Blanc, 1997. Early pulmonary cytokine

responses to zinc oxide fume inhalation. Environ. Res., 75: 7–11. doi:10.1006/enrs.1997.3765

Lademann, J., H. Weigmann, C. Rickmeyer, H. Barthelmes, H. Schaefer, G. Mueller, W. Sterry, 1999. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacol. Appl. Skin Physiol, 12: 247–256. doi:66249

Lam, C., J.T. James, R. McCluskey, S. Arepalli, R.L. Hunter, 2006. A Review of Carbon Nanotube Toxicity and Assessment of Potential Occupational and Environmental Health Risks. Crit. Rev. Toxicol, 36: 189–217. doi:10.1080/10408440600570233

Land area (sq. km) in Singapore [WWW Document], n.d. URL http://www.tradingeconomics.com/singapore/land-area-sq-km-wb-data.html (accessed 4.7.15).

Lanone, S., F. Rogerieux, J. Geys, A. Dupont, E. Maillot-Marechal, J. Boczkowski, G. Lacroix, P. Hoet, 2009. Comparative toxicity of 24 manufactured nanoparticles in human alveolar epithelial and macrophage cell lines. Part. Fibre Toxicol. 6, 14. doi:10.1186/1743-8977-6-14

Lin, W., Y. Huang, X.D. Zhou, Y. Ma, 2006. Toxicity of Cerium Oxide Nanoparticles in Human Lung Cancer Cells. Int. J. Toxicol, 25: 451–457. doi:10.1080/10915810600959543

Long, T.C., N. Saleh, R.D. Tilton, G.V. Lowry, B. Veronesi, 2006. Titanium dioxide (P25) produces reactive oxygen species in immortalized brain microglia (BV2): implications for nanoparticle neurotoxicity. Environ. Sci. Technol, 40: 4346–4352.

Maynard, A.D., E.D. Kuempel, 2005. Airborne Nanostructured Particles and Occupational Health. J. Nanoparticle Res., 7: 587–614. doi:10.1007/s11051-005-6770-9

Maynard, A.D., P.A. Baron, M. Foley, A.A. Shvedova, E.R. Kisin, V. Castranova, 2004. Exposure to carbon nanotube material: aerosol release during the handling of unrefined single-walled carbon nanotube material. J. Toxicol. Environ. Health A, 67: 87–107. doi:10.1080/15287390490253688

Medina, C., M.J. Santos-Martinez, A. Radomski, O.I. Corrigan, M.W. Radomski, 2009. Nanoparticles: pharmacological and toxicological significance: Nanoparticles. Br. J. Pharmacol, 150: 552–558. doi:10.1038/sj.bjp.0707130

Methner, M., L. Hodson, C. Geraci, 2009. Nanoparticle Emission Assessment Technique (NEAT) for the Identification and Measurement of Potential Inhalation Exposure to Engineered Nanomaterials — Part A. J. Occup. Environ. Hyg., 7: 127–132. doi:10.1080/15459620903476355

Methner, M.M., M.E. Birch, D.E. Evans, B.K. Ku, K. Crouch, M.D. Hoover, 2007. Identification and characterization of potential sources of worker exposure to carbon nanofibers during polymer composite laboratory operations. J. Occup. Environ. Hyg., 4: 125–130. doi:10.1080/15459620701683871

Nanofilm Technologies International Pte Ltd [WWW Document], n.d. URL http://www.nanofilm.com.sg/jszx_fcva.php (accessed 4.7.15).

NanoMaterials Technology [WWW Document], n.d. URL http://www.nanomt.com/ (accessed 4.7.15).

Nasterlack, M., A. Zober, C. Oberlinner, 2008. Considerations on occupational medical surveillance in employees handling nanoparticles. Int. Arch. Occup. Environ. Health, 81: 721–726. doi:10.1007/s00420-007-0245-5

Nikula, K.J., M.B. Snipes, E.B. Barr, W.C. Griffith, R.F. Henderson, J.L. Mauderly, 1995. Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam. Appl. Toxicol. Off. J. Soc. Toxicol, 25: 80–94.

Oberdörster, G., Z. Sharp, V. Atudorei, A. Elder, R. Gelein, W. Kreyling, C. Cox, 2004. Translocation of Inhaled Ultrafine Particles to the Brain. Inhal. Toxicol, 16: 437–445. doi:10.1080/08958370490439597

Paddle-Ledinek, J.E., Z. Nasa, H.J. Cleland, 2006. Effect of Different Wound Dressings on Cell Viability and Proliferation: Plast. Reconstr. Surg., 117: 110S–118S. doi:10.1097/01.prs.0000225439.39352.ce

Paik, S.Y., D.M. Zalk, P. Swuste, 2008. Application of a Pilot Control Banding Tool for Risk Level Assessment and Control of Nanoparticle Exposures. Ann. Occup. Hyg, 52: 419–428. doi:10.1093/annhyg/men041

Park, E.J., J. Choi, Y.K. Park, K. Park, 2008. Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells. Toxicology, 245: 90–100. doi:10.1016/j.tox.2007.12.022

Poon, V.K.M., A. Burd, 2004. In vitro cytotoxity of silver: implication for clinical wound care. Burns, 30: 140–147. doi:10.1016/j.burns.2003.09.030

Pourchez, J., V. Forest, N. Boumahdi, D. Boudard, M. Tomatis, B. Fubini, N. Herlin-Boime, Y. Leconte, B. Guilhot, M. Cottier, P. Grosseau, 2012. In vitro cellular responses to silicon carbide nanoparticles: impact of physico-chemical features on pro-inflammatory and pro-oxidative effects. J. Nanoparticle Res., 14. doi:10.1007/s11051-012-1143-7

Quantum Precision Instruments – Products [WWW Document], n.d. URL http://www.quantum-pi.com/tech.html (accessed 4.7.15).

Radomski, A., P. Jurasz, D. Alonso-Escolano, M. Drews, M. Morandi, T. Malinski, M.W. Radomski, 2005. Nanoparticle-induced platelet aggregation and vascular thrombosis. Br. J. Pharmacol, 146: 882–893. doi:10.1038/sj.bjp.0706386

Ramachandran, G., M. Ostraat, D.E. Evans, M.M. Methner, P. O'Shaughnessy, J. D'Arcy, C.L. Geraci, E. Stevenson, A. Maynard, K. Rickabaugh,

2011. A strategy for assessing workplace exposures to nanomaterials. J. Occup. Environ. Hyg, 8: 673–685. doi:10.1080/15459624.2011.623223

RANKINGS [WWW Document], n.d. URL https://www.edb.gov.sg/content/edb/en/why-singapore/about-singapore/facts-and-rankings/rankings.html (accessed 4.7.15).

Renwick, L.C., D. Brown, A. Clouter, K. Donaldson, 2004. Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. Occup. Environ. Med., 61: 442–447.

Renwick, L.C., K. Donaldson, A. Clouter, 2001. Impairment of alveolar macrophage phagocytosis by ultrafine particles. Toxicol. Appl. Pharmacol, 172: 119–127. doi:10.1006/taap.2001.9128

Sayes, C.M., R. Wahi, P.A. Kurian, Y. Liu, J.L. West, K.D. Ausman, D.B. Warheit, V.L. Colvin, 2006. Correlating nanoscale titania structure with toxicity: a cytotoxicity and inflammatory response study with human dermal fibroblasts and human lung epithelial cells. Toxicol. Sci. Off. J. Soc. Toxicol, 92: 174–185. doi:10.1093/toxsci/kfj197

Schlesinger, R.B., 1995. Toxicological Evidence for Health Effects from Inhaled Particulate Pollution: Does it Support the Human Experience? Inhal. Toxicol, 7: 99–109. doi:10.3109/08958379509014274

Schneider, T., Nordic Council of Ministers, 2007. Evaluation and control of occupational health risks from nanoparticles. Nordic Council of Ministers, Copenhagen.

Shi, H., R. Magaye, V. Castranova, J. Zhao, 2013. Titanium dioxide nanoparticles: a review of current toxicological data. Part. Fibre Toxicol. 10, 15. doi:10.1186/1743-8977-10-15

Soto, K., K. Garza, L. Murr, 2007. Cytotoxic effects of aggregated nanomaterials☆. Acta Biomater, 3: 351–358. doi:10.1016/j.actbio.2006.11.004

Suh, W.H., K.S. Suslick, G.D. Stucky, Y.H. Suh, 2009. Nanotechnology, nanotoxicology, and neuroscience. Prog. Neurobiol, 87: 133–170. doi:10.1016/j.pneurobio.2008.09.009

Sung, J.H., J.H. Ji, J.U. Yoon, D.S. Kim, M.Y. Song, J. Jeong, B.S. Han, J.H. Han, Y.H. Chung, J. Kim, T.S. Kim, H.K. Chang, E.J. Lee, J.H. Lee, I.J. Yu, 2008. Lung Function Changes in Sprague-Dawley Rats After Prolonged Inhalation Exposure to Silver Nanoparticles. Inhal. Toxicol, 20: 567–574. doi:10.1080/08958370701874671

Svensson, I., E. Artursson, P. Leanderson, R. Berglind, F. Lindgren, 1997. Toxicity in vitro of some silicon carbides and silicon nitrides: whiskers and powders. Am. J. Ind. Med., 31: 335–343.

Takenaka, S., E. Karg, C. Roth, H. Schulz, A. Ziesenis, U. Heinzmann, P. Schramel, J. Heyder, 2001. Pulmonary and Systemic Distribution of Inhaled Ultrafine Silver Particles in Rats. Environ. Health Perspect. Suppl, pp: 109-547.

Tran, C.L., D. Buchanan, R.T. Cull, 2000. INHALATION OF POORLY SOLUBLE PARTICLES. II. INFLUENCE OF PARTICLE SURFACE AREA ON INFLAMMATION AND CLEARANCE. Inhal. Toxicol, 12: 1113–1126. doi:10.1080/08958370050166796

Trop, M., M. Novak, S. Rodl, B. Hellbom, W. Kroell, W. Goessler, 2006. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J. Trauma, 60: 648–652. doi:10.1097/01.ta.0000208126.22089.b6

Vaughan, G.L., S.A. Trently, R.B. Wilson, 1993. Pulmonary response, in vivo, to silicon carbide whiskers. Environ. Res., 63: 191–201. doi:10.1006/enrs.1993.1140

Wang, B., W. Feng, M. Wang, T. Wang, Y. Gu, M. Zhu, H. Ouyang, J. Shi, F. Zhang, Y. Zhao, Z. Chai, H. Wang, J. Wang, 2008. Acute toxicological impact of nano- and submicro-scaled zinc oxide powder on healthy adult mice. J. Nanoparticle Res. Interdiscip. Forum Nanoscale Sci. Technol, pp: 263.

Wang, B., W.Y. Feng, T.C. Wang, G. Jia, M. Wang, J.W. Shi, F. Zhang, Y.L. Zhao, Z.F. Chai, 2006. Acute toxicity of nano- and micro-scale zinc powder in healthy adult mice. Toxicol. Lett, 161: 115–123. doi:10.1016/j.toxlet.2005.08.007

Wang, J., Y. Fan, 2014. Lung Injury Induced by TiO2 Nanoparticles Depends on Their Structural Features: Size, Shape, Crystal Phases, and Surface Coating. Int. J. Mol. Sci., 15: 22258–22278. doi:10.3390/ijms151222258

Warheit, D.B., T.R. Webb, C.M. Sayes, V.L. Colvin, K.L. Reed, 2006. Pulmonary instillation studies with nanoscale TiO2 rods and dots in rats: toxicity is not dependent upon particle size and surface area. Toxicol. Sci. Off. J. Soc. Toxicol, 91: 227–236. doi:10.1093/toxsci/kfj140

Welcome to Statistics Singapore [WWW Document], n.d. URL http://www.singstat.gov.sg/ (accessed 4.7.15).

Wesselkamper, S.C., L.C. Chen, T. Gordon, 2001. Development of pulmonary tolerance in mice exposed to zinc oxide fumes. Toxicol. Sci. Off. J. Soc. Toxicol, 60: 144–151.

Xiaoyong Deng, Qixia Luan, Wenting Chen, Yanli Wang, Minghong Wu, Haijiao Zhang, Zheng Jiao, 2009. Nanosized zinc oxide particles induce neural stem cell apoptosis. Nanotechnology, 20: 15101–15101.

Yang, H., C. Liu, D. Yang, H. Zhang, Z. Xi, 2009. Comparative study of cytotoxicity, oxidative stress and genotoxicity induced by four typical nanomaterials: the role of particle size, shape and composition. J. Appl. Toxicol. JAT, 29: 69–78. doi:10.1002/jat.1385

Zalk, D.M., S.Y. Paik, P. Swuste, 2009. Evaluating the Control Banding Nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J. Nanoparticle Res., 11: 1685–1704. doi:10.1007/s11051-009-9678-y

Zhang, R., Y. Dai, X. Zhang, Y. Niu, T. Meng, Y. Li, H. Duan, P. Bin, M. Ye, X. Jia, M. Shen, S. Yu, X. Yang, W. Gao, Y. Zheng, 2014. Reduced pulmonary function and increased pro-inflammatory cytokines in nanoscale carbon black-exposed workers. Part. Fibre Toxicol. 11. doi:10.1186/s12989-014-0073-1