***Task ID*:** **425.023**

***Project title*:**

Environmental Safety and Health (ESH) Impacts of Emerging Nanoparticles and Byproducts from Semiconductor Manufacturing - Preparation and Characterization of Nanoparticles

***Deliverable*:**

Report on the results on physicochemical and surface characteristics of Phase 1 NPs relevant to toxicity assessment

Background:

Numerous reports published in recent years indicate a growing concern for the potential toxicity of engineered nanomaterials (Balbus et al. 2007; Nel et al. 2006; Handy & Shaw, 2007). Toxicity research is a high priority for the semiconductor industry due to the fact that some nanoparticles (*e.g.* chemo-mechanical planarization (CMP) slurry particles) are currently used in semiconductor manufacturing, and various new nano-sized materials (nanowires, carbon nanotubes, immersion lithography nanoparticles) are being considered for upcoming manufacturing processes. Predicting the potential toxicity of emerging nanoparticles (NPs) will require hypothesis-driven research that elucidates how physicochemical parameters influence toxic effects on biological systems. Of particular concern are NPs of less than 0.1 μm that would escape normal mechanisms of cellular defense (Gwinn & Vallyathan, 2006; Stern & McNeil, 2008). The intrinsic capacity of NPs to penetrate biological tissue may in itself not be the primary cause of toxicity; rather surface properties of NPs may accentuate (or minimize) toxicity. These include high specific surface area, reactive surfaces, and adsorptive surfaces for other toxic chemicals. Contaminants can also accumulate in NPs via nano-capillary condensation (Kelvin effect) in the particle pores. NPs have very high surface curvatures, engendering high surface tensions and energies that might have unique effects on living cells. Reactive radical species can have prolonged lifetimes when sorbed onto NPs. There is a growing consensus that reactive oxygen species (ROS, composed primarily of hydroxyl radicals, hydrogen peroxide and superoxide) are a major contributing factor of NP toxicity (Gwinn & Vallyathan, 2006; Limbach et al., 2007). ROS are normally produced in and around living tissues; however, overproduction can lead to cell toxicity and loss of cell and tissue function.

Objective and key findings:

The goal of this project is to characterize the potential toxicity of current and future NPs and NP-byproducts of SC manufacturing. The information will be used to develop mechanistic hypotheses that will be applied to developing rapid toxicity assessment protocols applicable in the industrial workplace, as well as to predicting the ESH impacts of NPs based on physicochemical properties. Our hypothesis is that the size and size distribution of nanoparticles intrinsically makes them more adsorptive to external chemicals, and these surface molecules can contribute to the observed toxic effects of nanoparticles on cells.

The objective of this task is to investigate the physicochemical and surface characteristics of Phase 1 NPs relevant to toxicity assessment.

Preliminary results confirmed that contaminant retention by the selected inorganic oxide NPs is compound dependent. The retention affinity of the NPs decreased in the order: CeO_2 > Al_2O_3 > HfO_2. Adsorption on CeO_2 of the test compound considered (H_{2O}) seems to be due to strong chemisorption. In agreement with literature findings, the retention of contaminants on NPs was shown to be size dependent, as indicated by the increased retention observed for HfO_2 nanoparticles with decreasing particle size. These results indicate that small particles have a high capacity for adsorption and retention of secondary contaminants. Furthermore, positive and negative SIMS spectra were shown to provide a powerful tool to identify NP impurities including metals from fabrication and organics from unidentified sources.

Additional work focusing on the stability of NP dispersions in various biological media commonly utilized in toxicity testing confirmed significant NP aggregation. Polyacrylate dispersants were shown to be effective in minimizing NP aggregation in biological media at concentrations sufficiently low to avoid biological inhibition.

Method of Approach

The nanomaterials selected for study have been classified in two categories, namely, Phase I NPs and Phase II NPs. The project will initially focus on hafnium dioxide (HfO_2) NPs used in immersion photolithography, and silicon dioxide (SiO_2) NPs utilized as abrasives in CMP slurries (**Phase 1 NPs)**. Subsequently, the focus will be on other types of CMP-related primary and secondary NPs (*i.e.* cerium dioxide (CeO_2) and alumina (Al_2O_3)) (**Phase 2 NPs**).

SiO_2, CeO_2 and Al_2O_3 NPs in various sizes have been obtained from commercial sources. HfO_2 (100 nm) was also obtained from a chemical supplier. Additional nano-sized HfO_2 with lower average particle size were supplied by the Cornell University via a Sematech agreement. Selected physicochemical and surface characteristics of these nano-sized inorganic oxides were investigated using a variety of techniques including:

- Analysis of surface chemistry by secondary ion mass spectrometry (SIMS).

- Determination of specific area, active site density, and surface energetics for selective adsorption to assess the NP surface ability to concentrate and retain bulk contaminants.

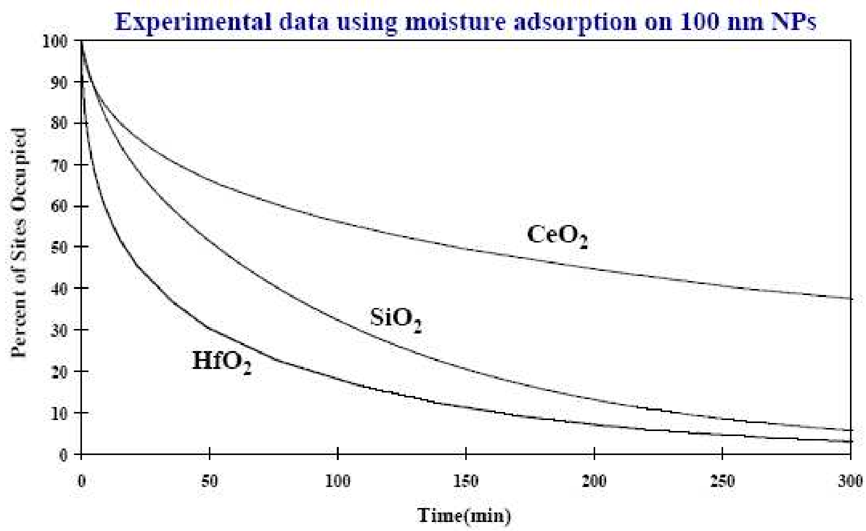
- Transmission- and scanning electron microscopy (TEM and SEM) to characterize nanoparticle morphology and particle size in dry conditions.

- Particle size distribution in aqueous media using dynamic light scattering detection (DLS).

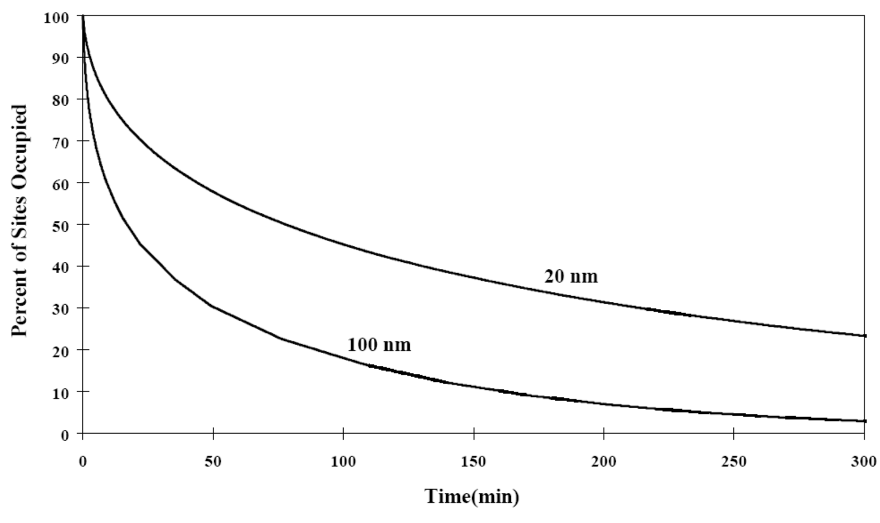
- Measurement of Zeta potential as an index of NP dispersion stability.

Technical Results and Data:

The Figure below is a comparison of the dynamics of surface cleaning for HfO_2, SiO_2, and CeO_2. The cleaning is measured by monitoring the desorption of moisture from the surface and clean up of the occupied sites. The results show that HfO_2 surface is the easiest to clean and CeO_2 surface is the most difficult one for surface site cleaning.



The results also indicate that the adsorption and desorption of contaminants are particle size dependent. Using moisture adsorption as an indicator of the strength of the surface sites and their adsorption tendency, the results in the Figure below show that HfO_2 particles with average size of 20 nm clean much more slowly than those on the particles with the average particle size of 100 nm. This indicates that nano-particles surfaces are more active and harder to de-contaminate.



Surface Characterization by SIMS. Characterization of surface chemistry by SIMS ToF was undertaken at the University of Washington. Positive and negative SIMS spectra were shown to provide a powerful tool to identify NP impurities including metals from fabrication and organics from unidentified sources. As an example, SIMS was utilized to investigate the surface composition of four different batches of HfO_2 including a micron-sized sample and three additional samples of nano-sized HfO_2 varying in average particle size (Table 1). Human toxicity as well as ecotoxicity studies indicated that only one of the four HfO_2 samples (NP1) was inhibitory and that toxic effect of that HfO_2 sample could not be correlated with particle size. Interestingly, SIMS analysis studies showed several impurities in the toxic HfO_2 sample (e.g. bromine containing residue) that were absent in the non-toxic samples.

Table 1. Impurities detected in HfO_2 samples obtained from various suppliers using SIMS ToF. Note: "+" represents presence of listed fragment. "++" and "+++" are used to indicate relative amounts of listed fragments within row and cannot be used to compare rows one to another.

mass	ID	Ref Micron	NP1 20 nm	NP2 1-2 nm	NP3 100 nm
27	Al	+	+		+
28	CH_2N	+	++		++
30	CH_4N	+	+		+
40	Ca	++			+
45	C_2H_5O	++		++	+
46	C_2H_6O	+		+	+
52	C_3H_2N		+		+
55	Fe	+			+
58	Ni		+		
78	$C_2H_6O_3$		+		
90	Zr	++	+		+
118	$C_5H_{12}NO_2$	+		+	+
135	$C_9H_{11}O$	++		++	+
161	$C_{11}H_{13}O$	++		+++	+

Future studies will evaluate the toxic effects of the materials selected with and without surface contamination by Cu and organics typically present in the CMP and post-CMP cleaning processes. Copper is highly inhibitory to many microorganisms and higher aquatic organisms (Gerhardt et al. 1993; Roesijadi, 1992), but this metal displays low toxicity against human cells.

Therefore, arsenic will also be used as a model contaminant of CMP nanoparticles. The results will be on interest to SRC companies because gallium arsenic alloys are being considered for introduction in semiconductor manufacturing. Planarization of GaAs should be expected to lead to interactions between arsenic and abrasive NPs in the CMP slurries.

Dispersion of NPs in biological media utilized for toxicity testing is very challenging (Sager et al. 200; Schulze et al. 2008). Our results confirmed that the CeO_2 nanoparticles (average particle size determined by TEM= 20 nm) underwent very significant aggregation in two media commonly used in toxicity tests with human cells, Mitochondrial Toxicity Test (MTT) medium and Hank's Buffered Salt Solution (HBSS) (Figure 1).

Testing the impact of material size on toxicity will require effective dispersion of the NP in the aqueous media. This project will investigate various methods to functionalize NP surfaces using biocompatible ligands in order to promote the stability of NP dispersions and prevent aggregation. Initial studies will consider surface modification by poly-acrylates, thiol-terminated polyethylene glycols (PEGs), and amino acids such as lysine. Preliminary results confirm that polyacrylates are very effective in minimizing NP aggregation in biological media at concentrations which are sufficiently low to avoid biological inhibition. Lysine was also an effective dispersant in tests with HfO_2.

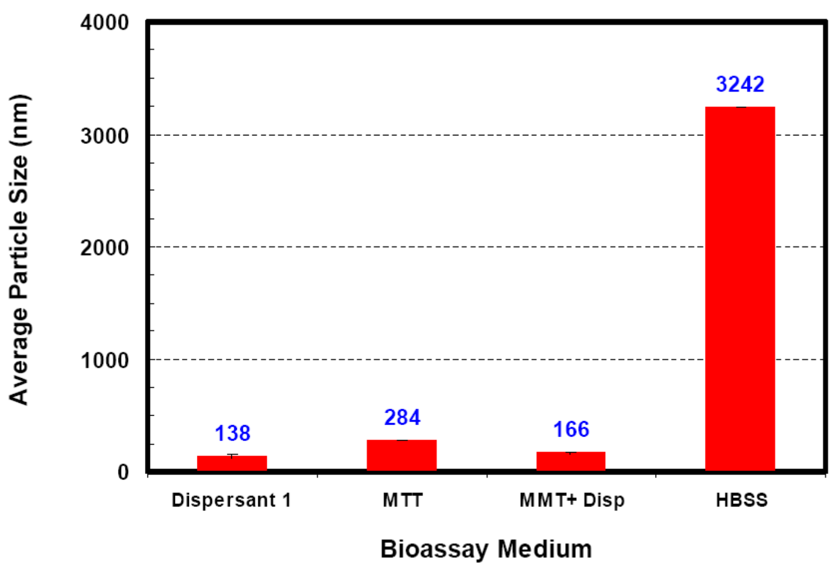


Fig. 1. Average particle size distribution of HfO_2 nanoparticles in various biological media in the presence and absence of a polyacrylate dispersant. MTT= Biological medium used in the Mitochondrial Toxicity Test. HBSS= Hank's Buffered Salt Solution used to culture human cells in various toxicity tests.

NP size fractionation. Both NP size and NP surface contaminants have been hypothesized to contribute to the toxic effects of NPs. Testing the impact of particle size on NP toxicity requires the use of NPs with similar surface chemistry. In order to minimize variations in surface chemistry, commercial inorganic oxide samples were fractionated by ultra-centrifugation. This approach proved successful in the separation of CeO_2 sub-samples of with a narrow particle size distribution (Figure 2).

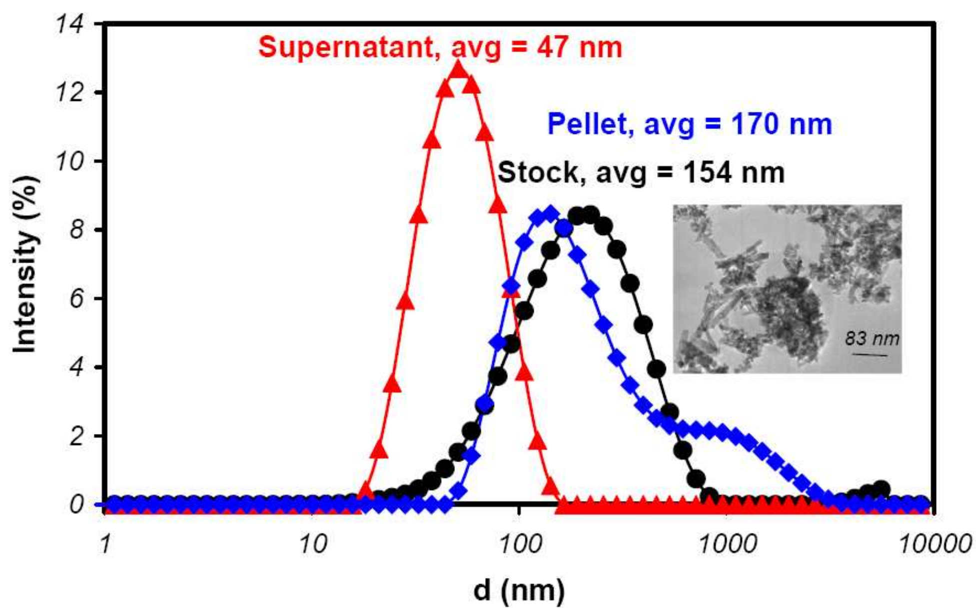


Fig. 2. Size fractionation CeO_2 nanoparticles by centrifugation (4500 rpm, 20 min).

REFERENCES

1. **Balbus et al.** 2007. Meeting report: Hazard assessment for nanoparticles - Report from an interdisciplinary workshop. Environ. Health Perspec. **115:**1654-1659.
2. **Gerhardt et al.** 1993. Review of impact of heavy-metals on stream invertebrates with special emphasis on acid conditions. Water Air Soil Pollut. **66**(3-4):289-314**.**
3. **Gwinn et al.** 2006. Nanoparticles: Health effects - Pros and cons. Environ. Health Perspec. **114:**1818-1825.
4. **Handy & Shaw.** 2007. Toxic effects of nanoparticles and nanomaterials: Implications for public health, risk assessment and the public perception of nanotechnology. Health Risk Soc. **9:**125-144.

5. **Limbach et al.** 2007. Exposure of engineered nanoparticles to human lung epithelial cells: Influence of chemical composition and catalytic activity on oxidative stress. Environ. Sci. Technol. **41:**4158-4163.
6. **Nel et al.** 2006. Toxic potential of materials at the nanolevel. Science **311**(5761): 622-627.
7. **Roesijadi, G.** Metallothioneins in metal regulation and toxicity in aquatic animals. 1992. Aquatic Toxicol. **22**(2):81-114.
8. **Sager et al.** 2007. Improved method to disperse nanoparticles for in vitro and in vivo investigation of toxicity. Nanotoxicol. **1**(2):118-129.
9. **Schulze et al.,** Not ready to use - overcoming pitfalls when dispersing nanoparticles in physiological media. Nanotoxicology, 2008. **2**(2): p. 51-U17.
10. **Stern & McNeil.** 2008. Nanotechnology safety concerns revisited. Toxicol. Sci. **101:**4-21.