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

<u>Tasks 425.023 and 425.024</u>

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Cost Share (other than core ERC funding):

- $80k from UA Water Sustainability Program

Overall Objectives

- Characterize toxicity of current and emerging nanoparticles (NP) & NP byproducts
- Develop new rapid methodologies for assessing and predicting toxicity

ESH Metrics and Impact

1. *Reduction in the use or replacement of ESH-problematic materials*

   This project will evaluate the toxicity of various types of nanoparticles utilized or considered for application in semiconductor manufacturing, and the impact of manufacturing steps on their toxicity. This information can assist in selecting materials which are candidates for replacement or use reduction.

2. *Reduction in emission of ESH-problematic material to environment*

   The knowledge gained can be utilized to modify the manufacture of nanoparticles so that they have a lowered toxicity and thus a lowered environmental impact.

Surface Physical Characterization

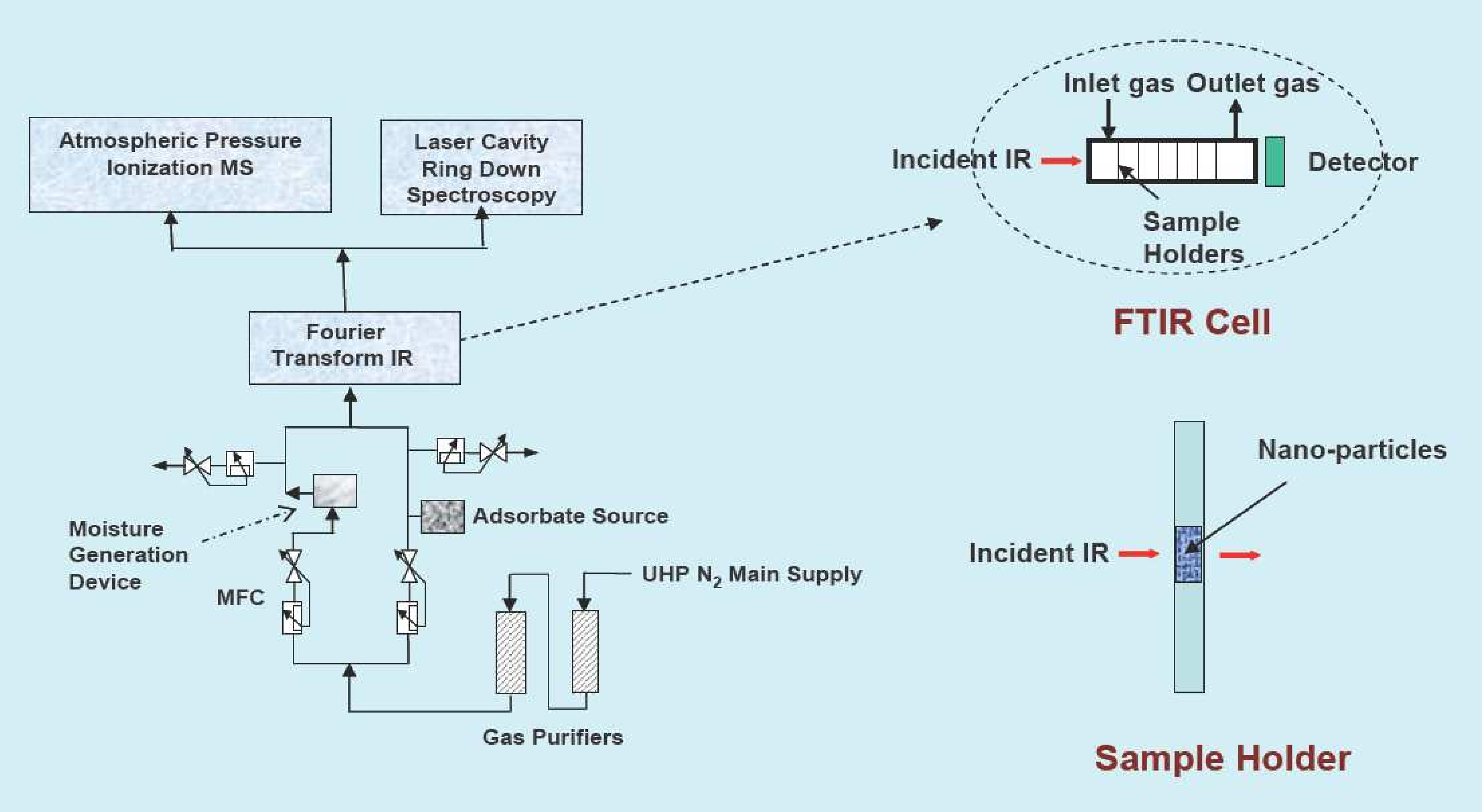
Hypothesis: The size and size distribution of nanoparticles intrinsically makes them more adsorptive to external chemicals, and these surface molecules lead to the observed toxic effects of nanoparticles on cells.

Surface Physical Characterization

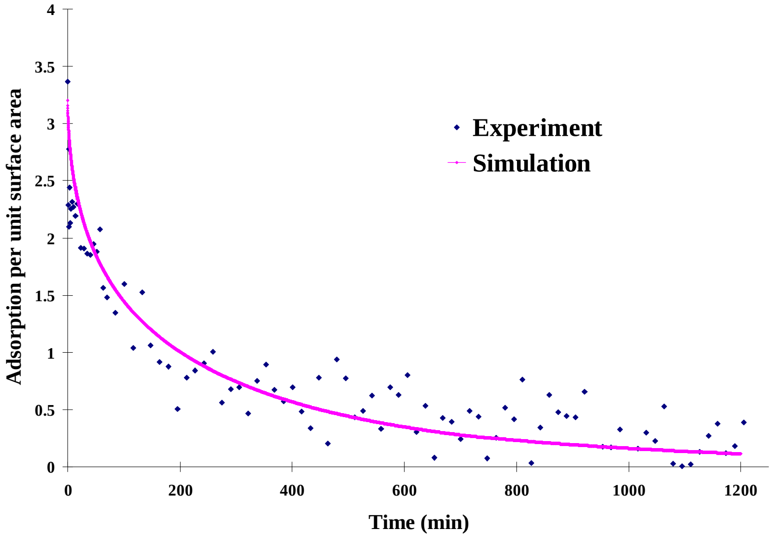
- **Particle size distribution (dynamic light scattering)**
- **Specific area (area/volume or area/mass of NP)**
- **Active site density; site energetics**
- **Physical adsorption vs chemical adsorption**
- **Ability of the surface to concentrate bulk contaminants (selective adsorption)**
- **Retention of contaminants**

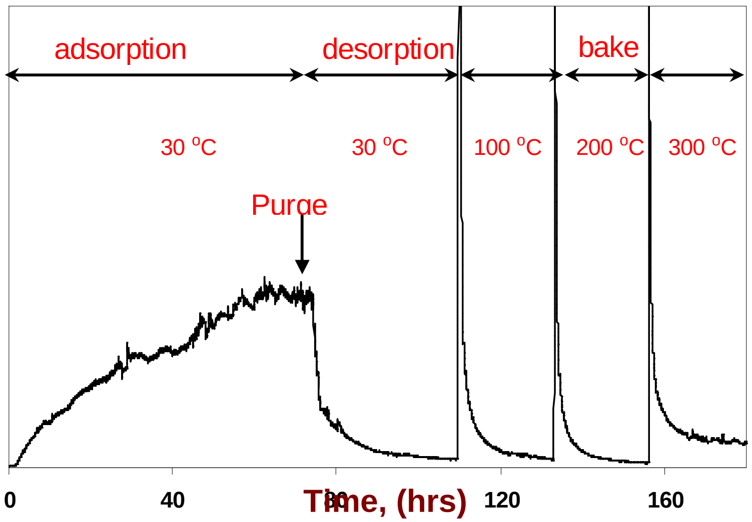
Surface Physical Characterization

Objective: **determine surface ability to concentrate and retain bulk contaminants. Key parameters are specific area, active site density, and surface energetics for selective adsorption**



Experimental Method & Typical Results



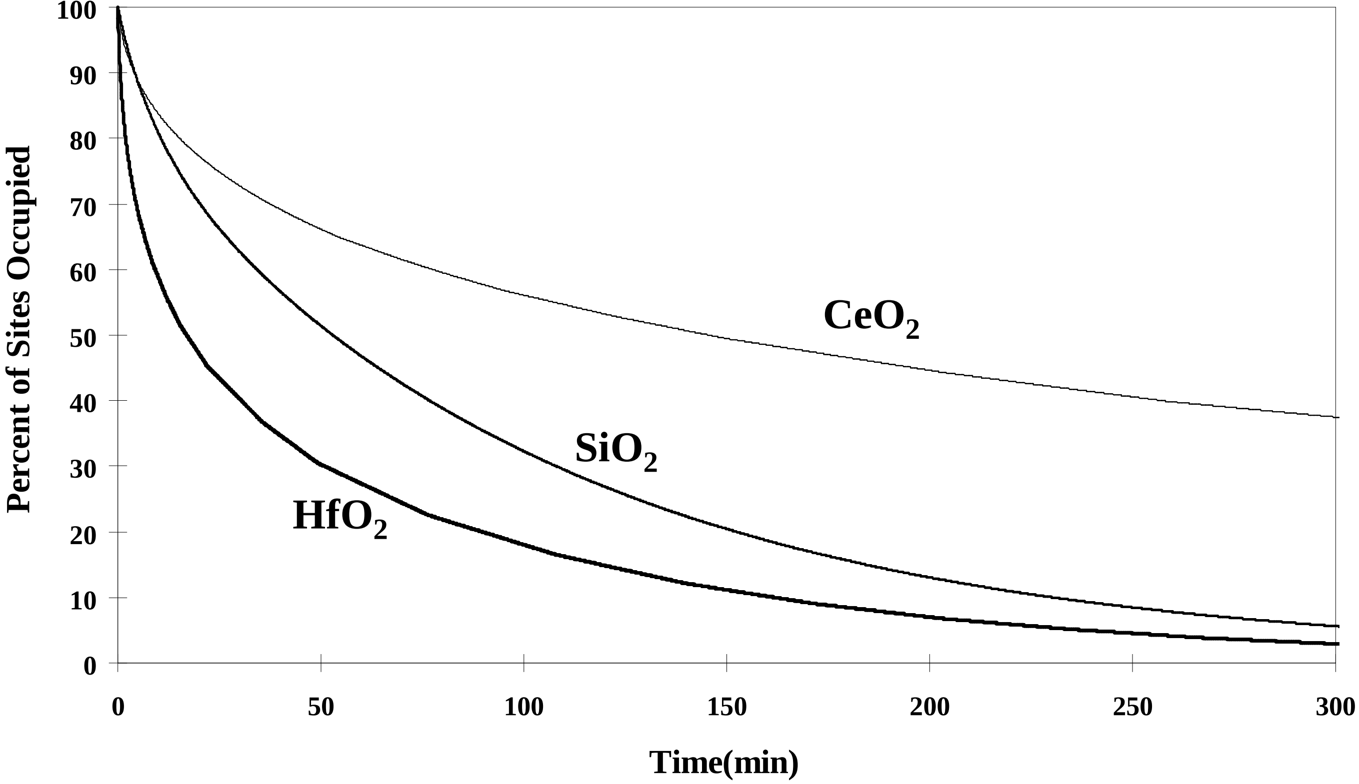


- **Physical adsorption of inert adsorbent (similar to BET isotherm) for area measurement**
- **Chemical adsorption of reactive adsorbent for measuring site density**

- **Temperature-Programmed Interaction (TPI) for measuring site energetics**

Comparison of Surface Activity of Different NP Materials

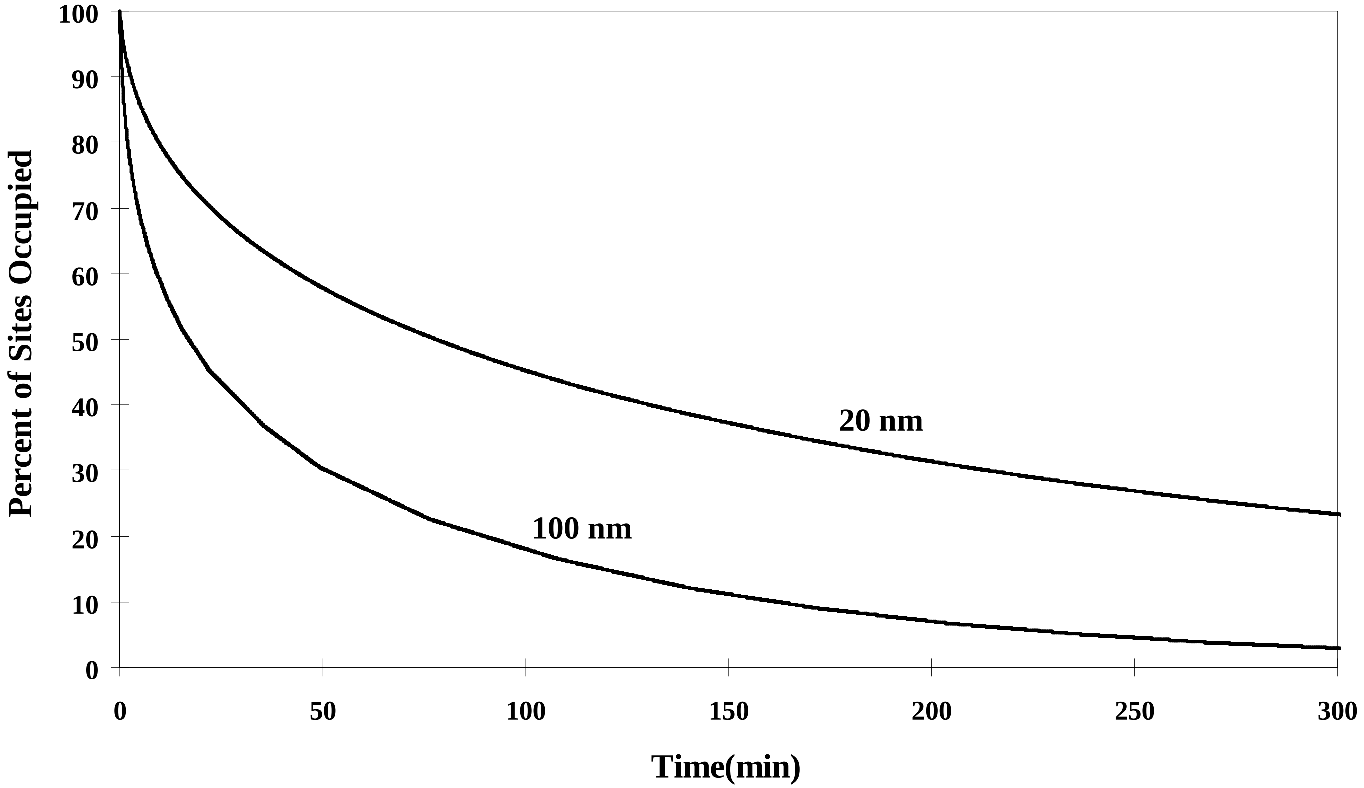
Experimental data using moisture adsorption on 100 nm NPs



Contamination retention is compound dependent: highest for CeO_2 and lowest for HfO_2; adsorption on CeO_2 seems to be strong chemisorption

NPs Retention of Contaminants

Dynamics of Moisture Desorption



Contamination retention of NPs is size dependent (smaller NPs show higher retention)

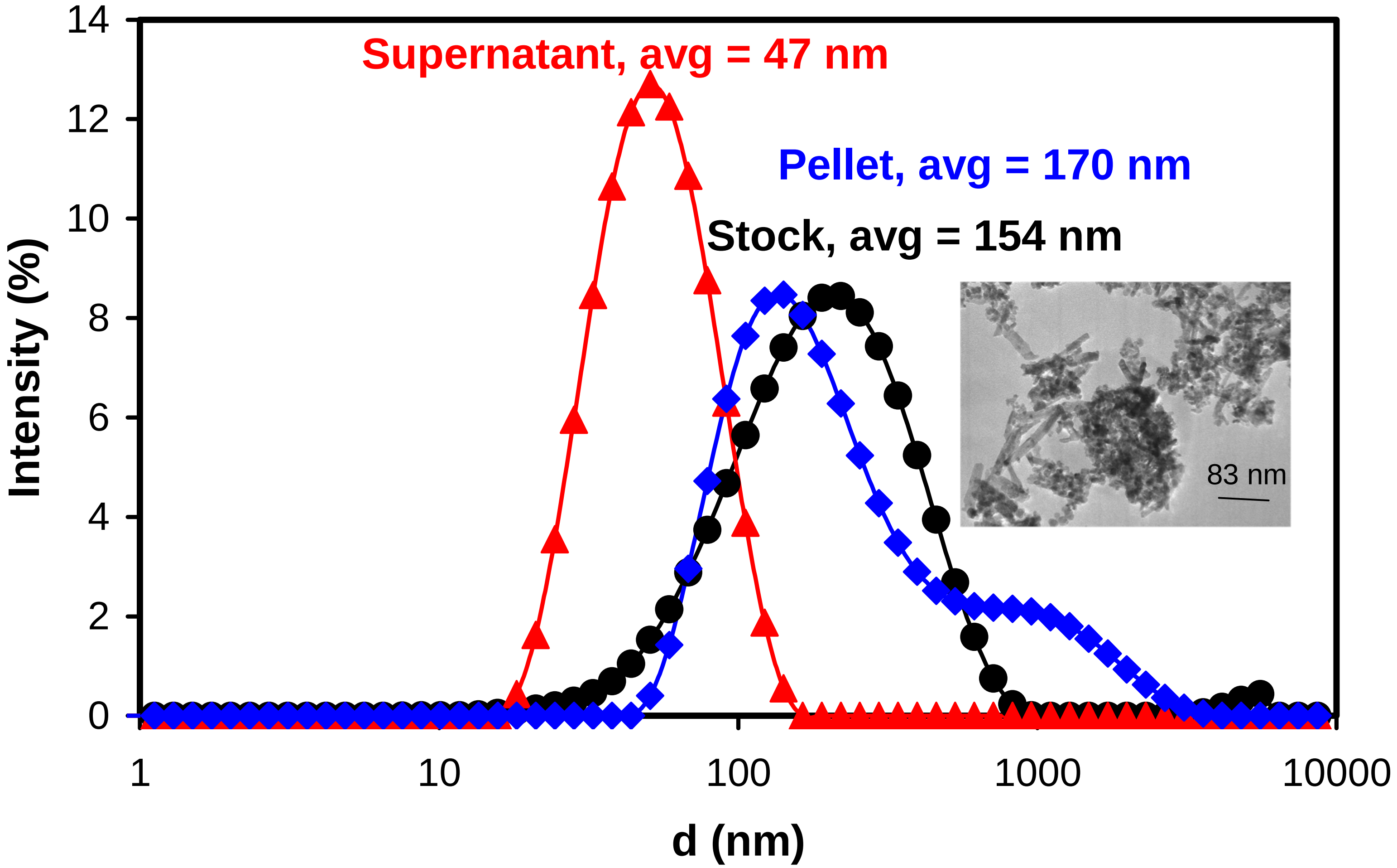
Surface Characterization

	Particle Size	Adsorption Rate Coeff.	Desorption Rate Coeff.	Active Site Density	Adsorption Capacity
	d_p (nm)	k_a ($cm^3\ mol^{-1}\ s^{-1}$)	k_d (s^{-1})	S_0 (mol/cm^2)	C_{s0} (mol/cm^2)
HfO_2	20	3.30E+08	2.4	7.00E-10	6.56E-10
HfO_2	100	8.00E+08	0.8	2.50E-10	2.48E-10
SiO_2	20	5.30E+08	360	2.00E-08	2.74E-09
CeO_2	20	3.00E+08	1	8.75E-10	8.49E-10

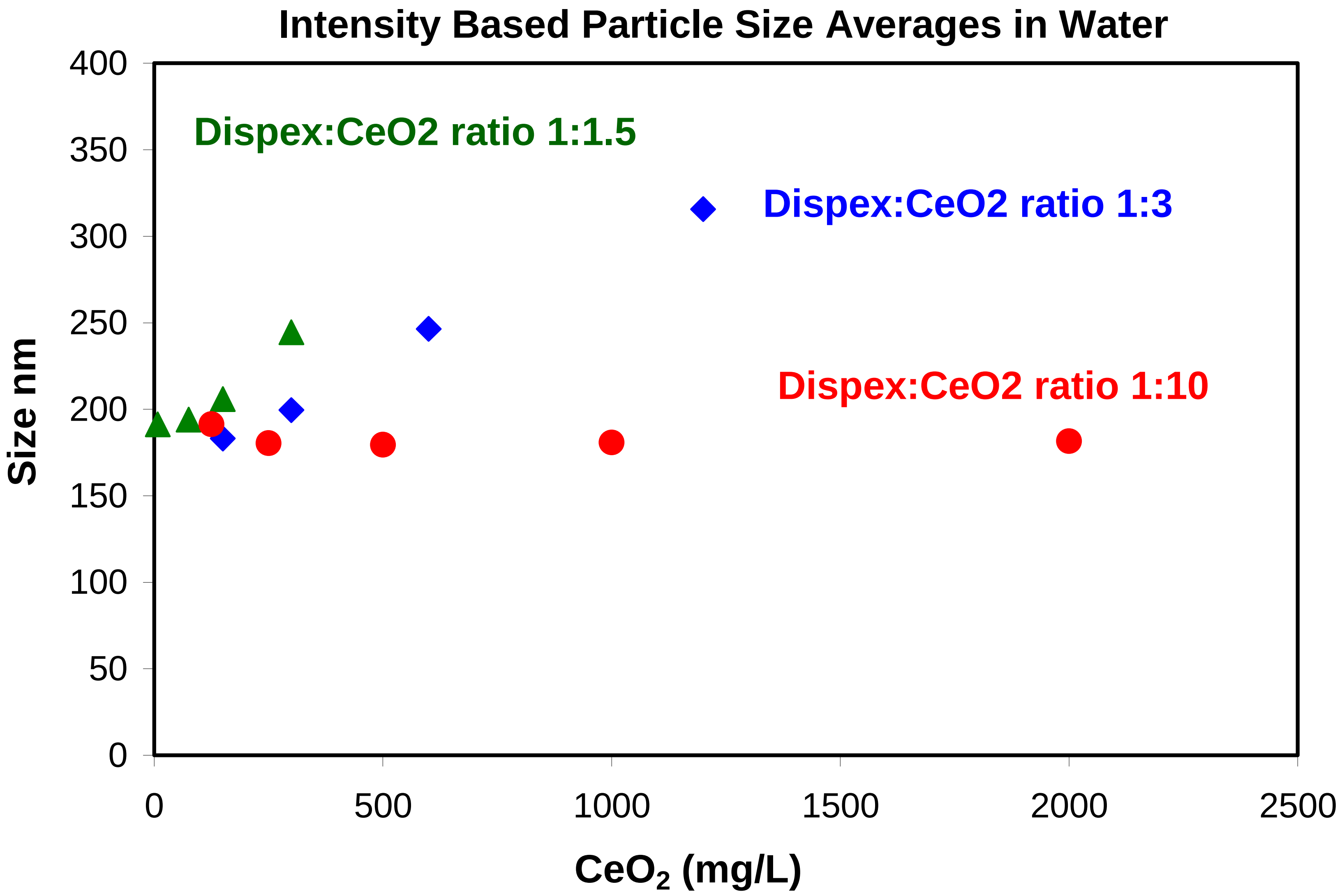
- **Small HfO_2 particles adsorbed contaminants more energetically than larger particles *(higher activation energy)***
- **Small particles have higher *capacity* for adsorption and retention of secondary contaminants**

Fractionation of CeO_2 by Centrifugation

Fractioning CeO_2 2g/L Eppendorf Centrifuge 4500 rpm



Role Surfactant Conc. on CeO$_2$ NP Size



Impact Biological Media on NP Dispersions

Intensity Based Particle Size Averages in Water (DLS)
(units = nm)

MEDIUM	MATERIAL		Comment
	HfO_2	CeO_2	
MQ Water	359 ± 12	1741 ± 275	
MQ Water + dispex	138 ± 2	209 ± 25	
MTT	284 ± 2		MTT = mitochondrion toxicity test medium
HBSS	3242 ± 270		HBSS = Hanks' Balanced Salt Solutions
DMEM	593 ± 252		DMEM = Dulbecco's Modified Eagle Medium (+25KBS, no HCO3)
Microtox	901 ± 406	236 ± 21	

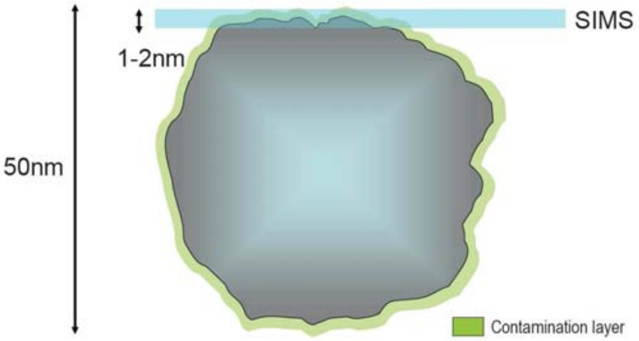
Surface Chemical Characterization

The University of Washington has a strong campus resource facility permitting us to perform state-of-the-art nanoparticle surface analysis. Instrumentation that is available for this purpose includes:

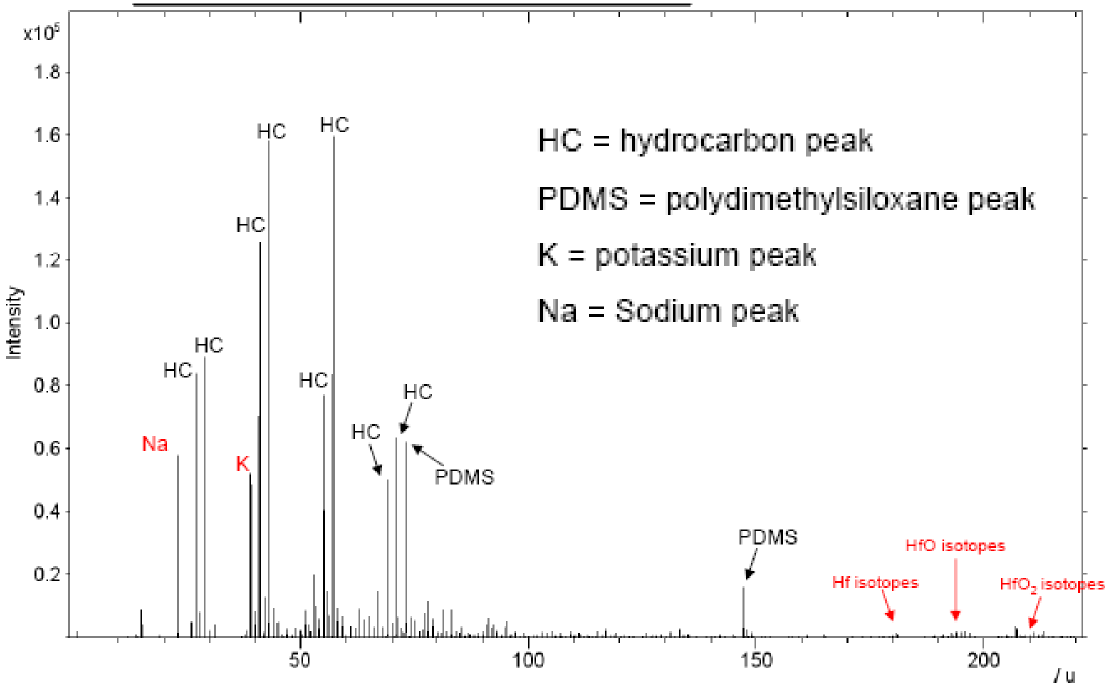
- Electron spectroscopy for chemical analysis (ESCA)
- Secondary ion mass spectrometry (SIMS)
- Surface plasmon resonance (SPR)
- Atomic force microscopy (AFM)
- Sum Frequency Generation (SFG)
- Attenuated Total Reflectance IR (ATR-IR)

Secondary Ion Mass Spectrometry (SIMS) Time-of-flight (ToF) SIMS; Static SIMS

- Probably the most information-rich of the modern surface analysis methods
- Various organic/inorganic contaminants detected on the surface of HfO_2 NPs



- Positive and negative spectra can be used to identify impurities including metals from fabrication or organics from unidentified sources



Nanoparticle Impurities – ToF SIMS

Positive Spectra Impurities

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	$C_{11}H_{13}O$	++		+++	+

"+" 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.

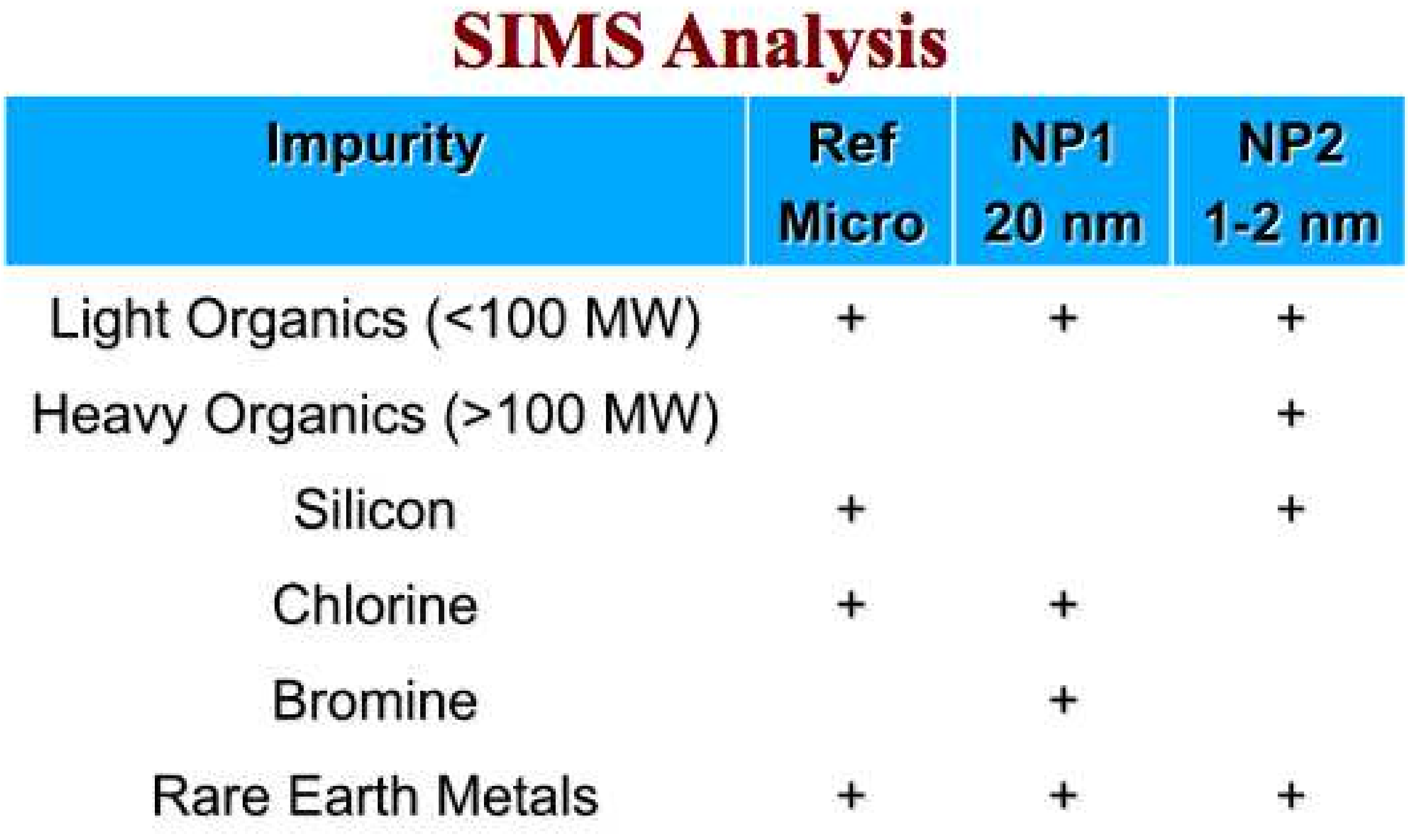
Nanoparticle Impurities – ToF SIMS

Negative Spectra Impurities

mass	ID	Ref Micron	NP1 20 nm	NP2 1-2 nm	NP3 100 nm
19	F	+++	+	++	++
26	CN	+	++		+
31	P		+		
35	Cl	+++	+	+	++
47	PO	+	++		
51	ClO	+			
59	$C_2H_3O_2$	+		++	
78	C_3H_7OF		+		
78.96	PO_3		+		
78.92	^{79}Br	+	++		
81	^{81}Br	+	++		
104	$C_3H_8N_2O_2$		+		
127	I	+			
205	$C_{13}H_{19}NO$			+	

"+" 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.

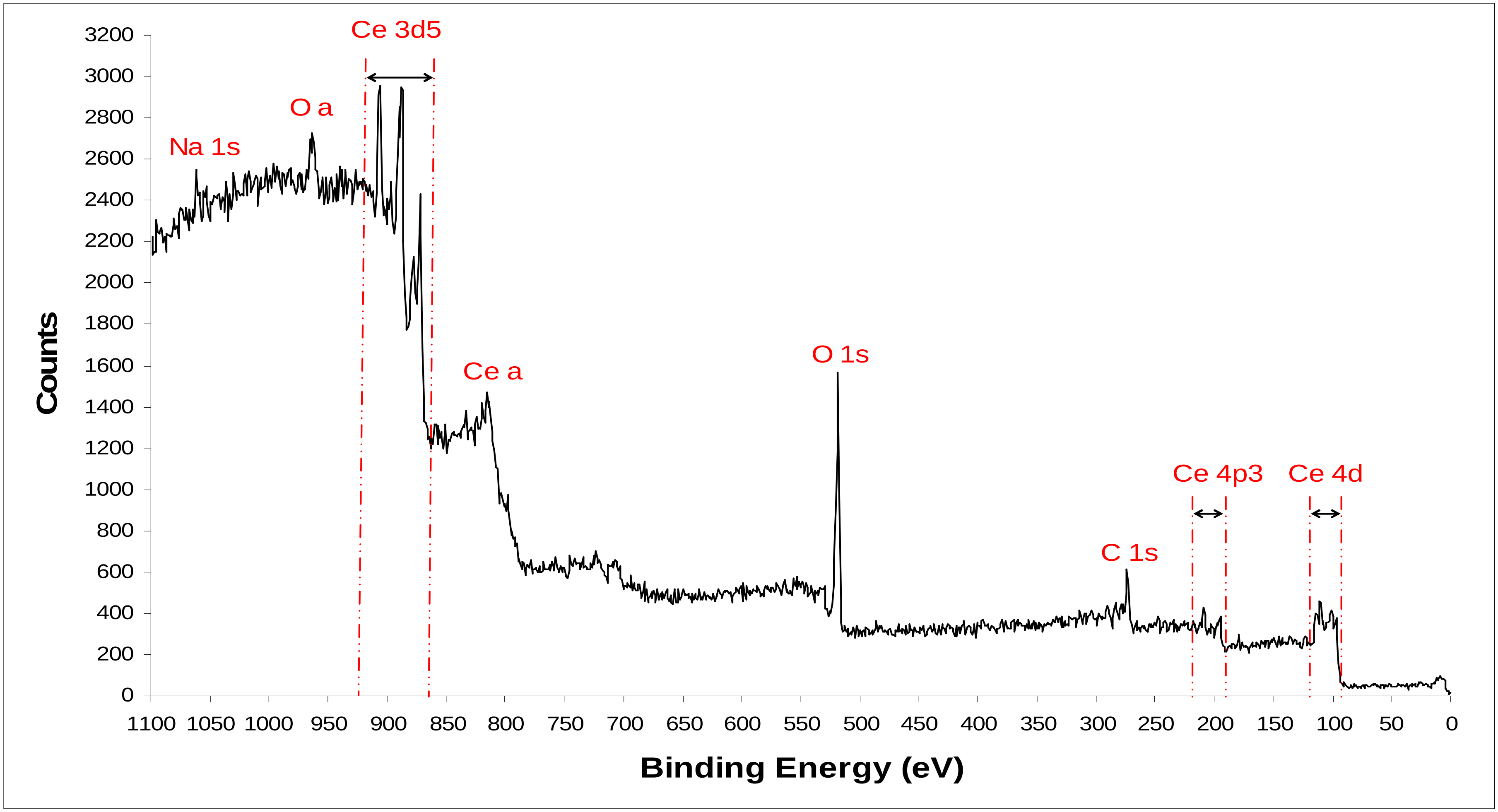
Surface Characterization Summary/Preliminary Conclusions



SIMS Analysis

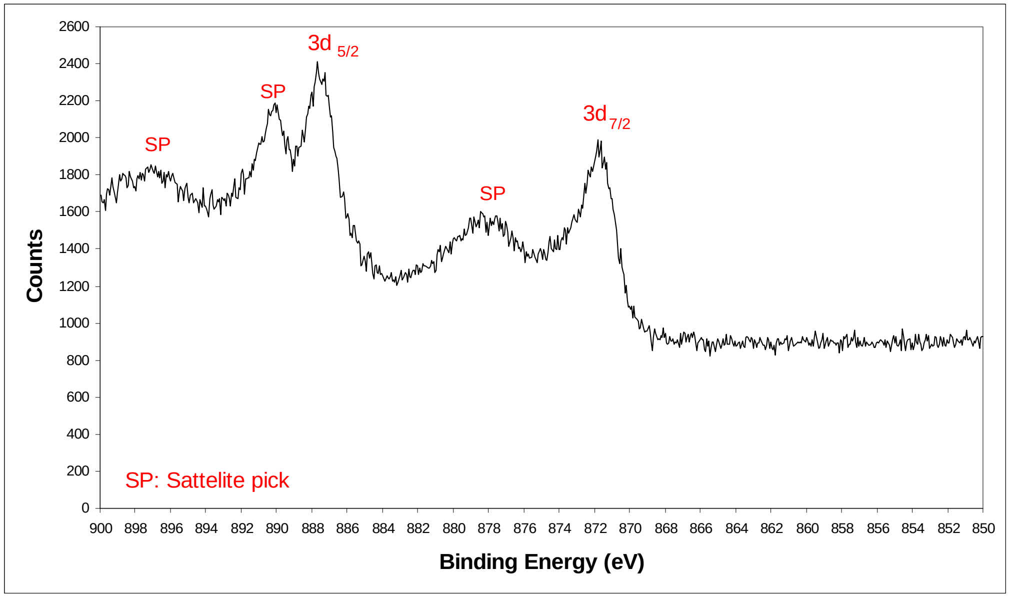
Impurity	Ref Micro	NP1 20 nm	NP2 1-2 nm
Light Organics (<100 MW)	+	+	+
Heavy Organics (>100 MW)			+
Silicon	+		+
Chlorine	+	+	
Bromine		+	
Rare Earth Metals	+	+	+

Catechol Treated CeO$_2$ XPS Spectra

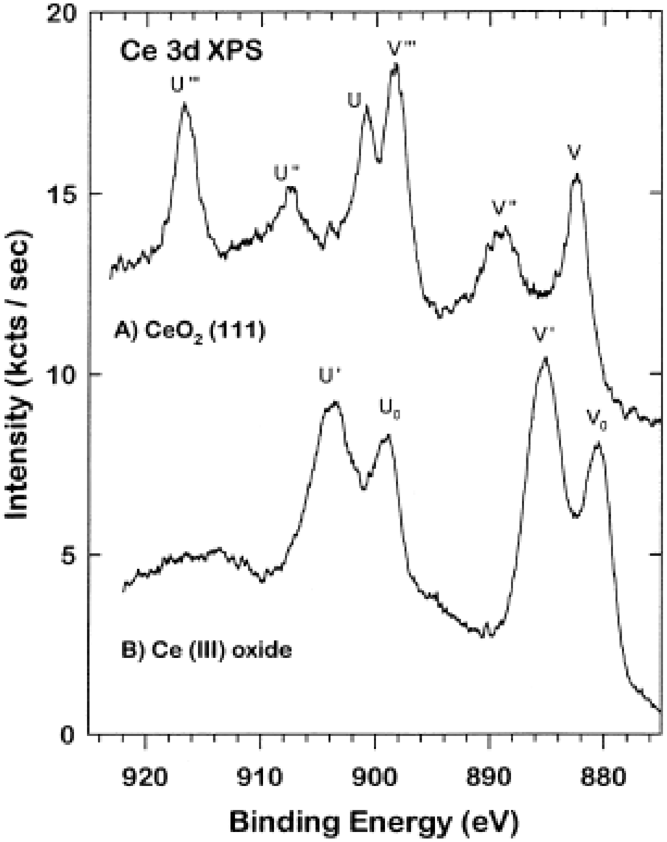


Sodium, carbon, cerium and oxygen were observed in the spectrum

CeO$_2$ Core Level XPS Spectra Comparison



High resolution XPS spectra of catechol treated CeO$_2$



Ce 3d core level photoemission spectra

from (A) CeO$_2$ (111), (B) Ce (III) oxide*

*** D.R. Mullins, S.H. Overbury, D. R. Huntley. Surface Science 409 (1998) 307-319.**

Surface Chemistry Results and Future Plans

- Our central hypothesis about the presence of surface contaminant species and high surface adsorptiveness of these nanoparticles is supported by our data.
- Comparison between Ce3d photoemission spectra of catechol treated CeO_2 and literature suggests that sample is in Ce4+ state.
- It has been shown in the literature that X-ray emission might have an effect on the oxidative state of the sample.
- In order to find the oxidative state of a pristine sample, the effect of x-ray on CeO_2 nanoparticles should be investigated.

Toxicity Assessment and Prediction

Objectives

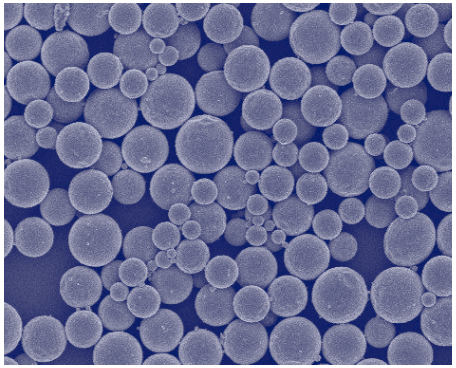
- Establish role for reactive oxygen species (ROS) and oxidative stress as a potential marker for NP toxicity assessment

- Develop predictable models of toxicity based on physico-chemical properties elucidated by advanced surface analysis techniques

- Validate toxicity assessments and predictions with organ skin cultures (and advanced lung cultures)

Materials

- Nanoparticles



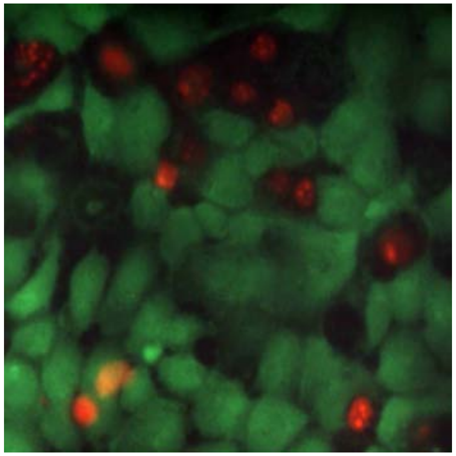
  Hafnium Oxide (HfO_2), immersion lithography

  Silica Oxide (SiO_2), CMP

  Ceria Oxide (CeO_2), CMP

  Others (Al_2O_3, carbon and germanium- nanotubes, quantum dots *etc*)

- Biological targets



  Human skin cell line (HaCat)

  Human lung epithelial cell line (16HBE14o-)

  Human foreskin rafted organ culture (ROC)

  Bacterium (*Vibrio fischeri*) Microtox test

  Others (methanogens, bacterial cultures, yeast *etc*)

Methods

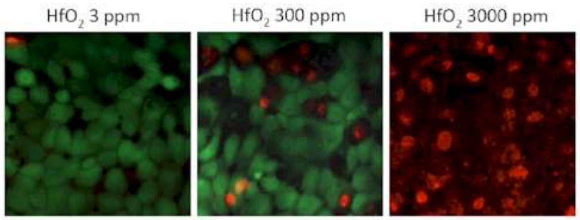
- Main Toxicity Tests Utilized

  Live/Dead Assay with HaCat Skin Cell Line (HaCat)

  Mitochondrial Toxicity test (MTT) (ureter cells)

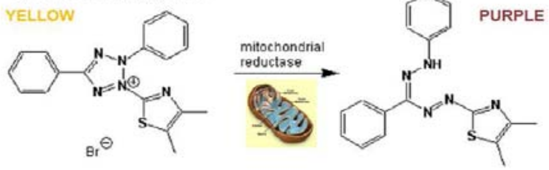
  Microtox (*Vibrio fischeri*)

  Methanogenic Activity



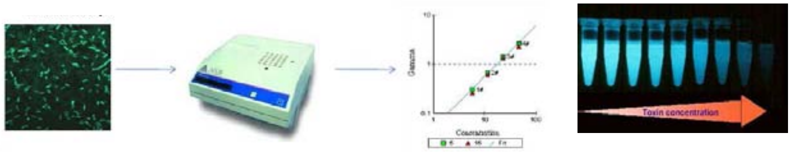
Live: calcein AM) Dead: ethidium homodimer-1

[redacted]



3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

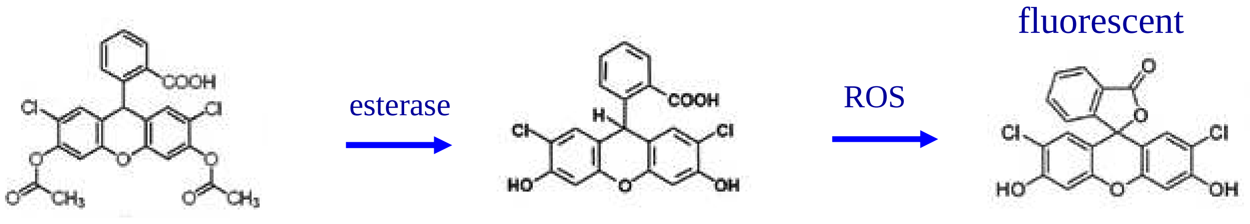
purple formazan



- Chemical: Reactive Oxygen Species (ROS) Production

  Detection of fluorescent ROS-sensitive dye

Fluorescence spectrometer



2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA)

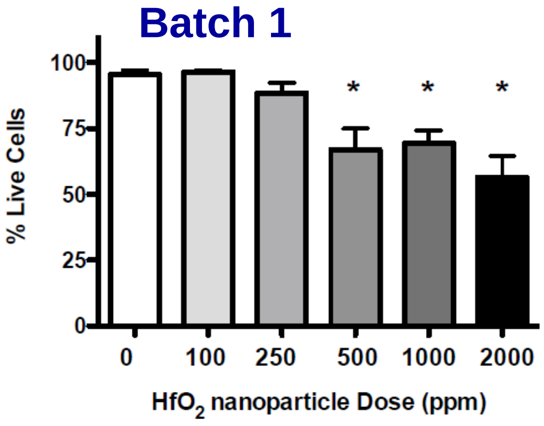
2′,7′-dichlorodihydrofluorescein (DCFH)

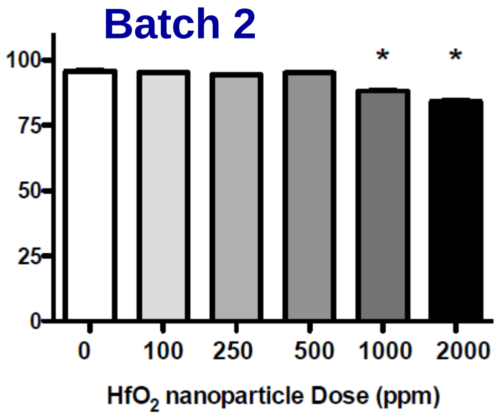
2′,7′-dichlorofluorescin (DCF)

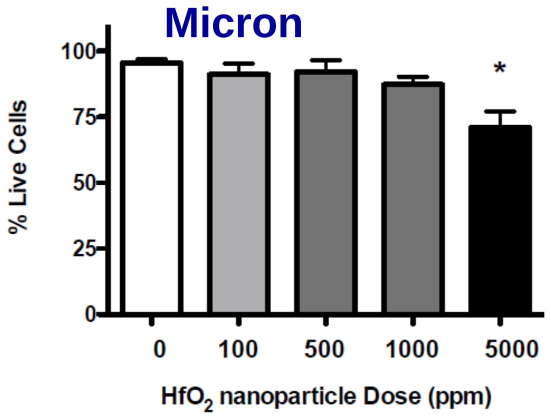
Results on HfO_2

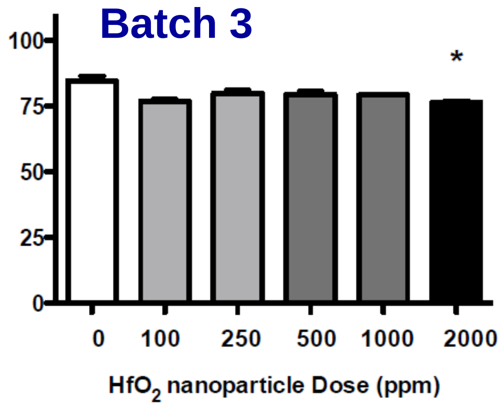
Four distinct batches of hafnium oxide tested. Example Live/Dead test (HaCat skin cells)

Batch	Measured	Manufact. Reported
	------ avg size (nm) ------	
Batch 1	**360**	**20**
Batch 2	**224**	**2**
Batch 3	**169**	**100**
Micron	**6000**	**< 44,000**





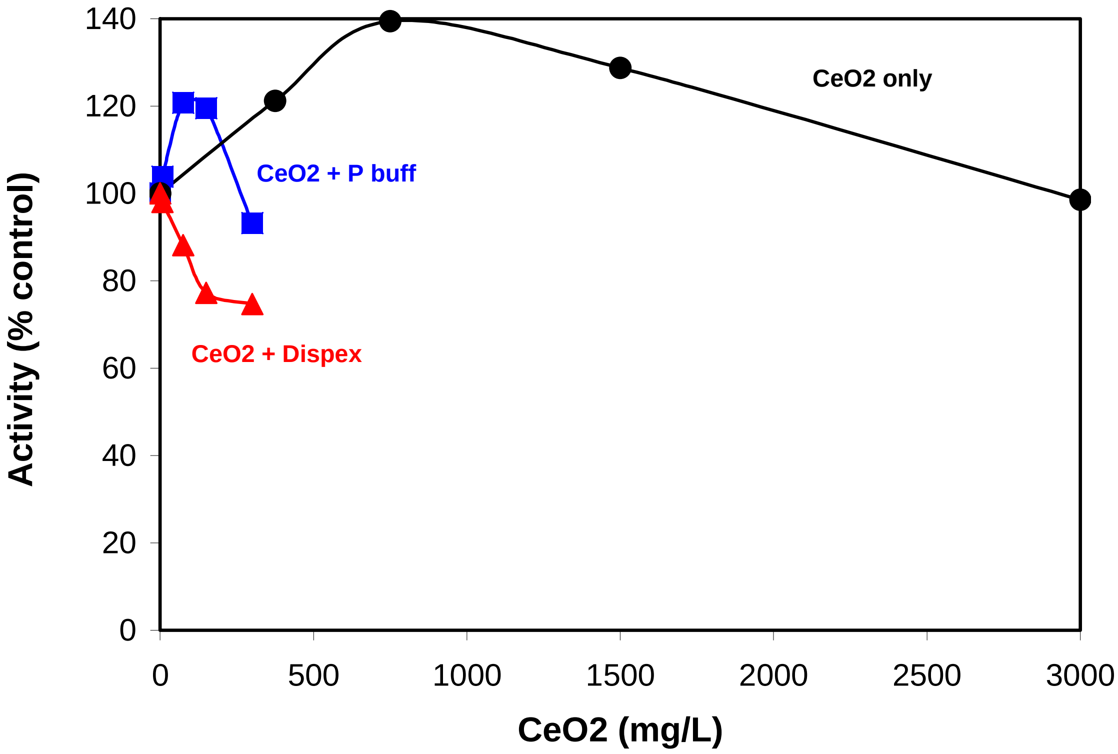




Results on CeO_2

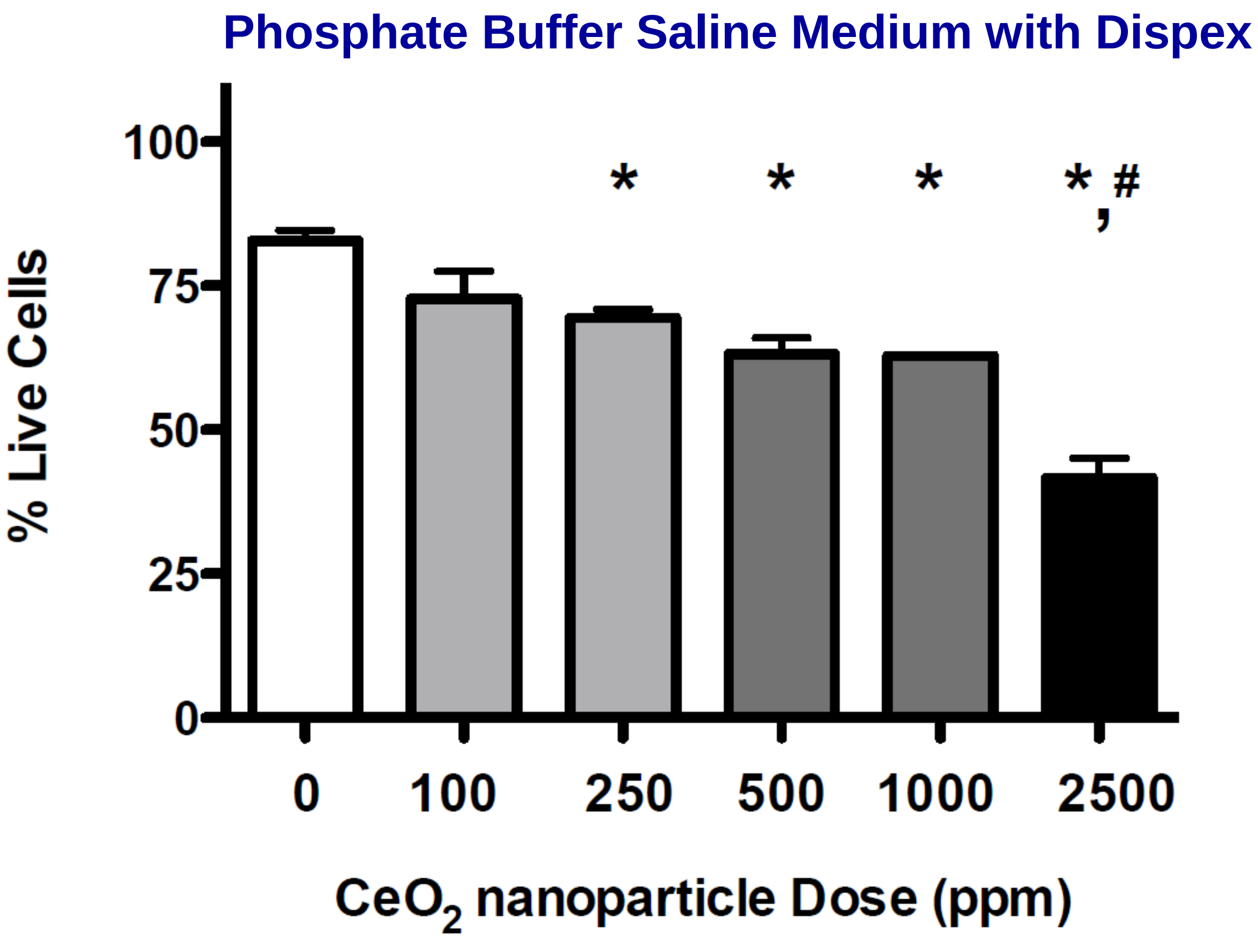
Cerium oxide (MTI, "20 nm"). Example Microtox Test

Prep.	Measured avg size (nm)
Water	**1741**
+ Dispex	**183**



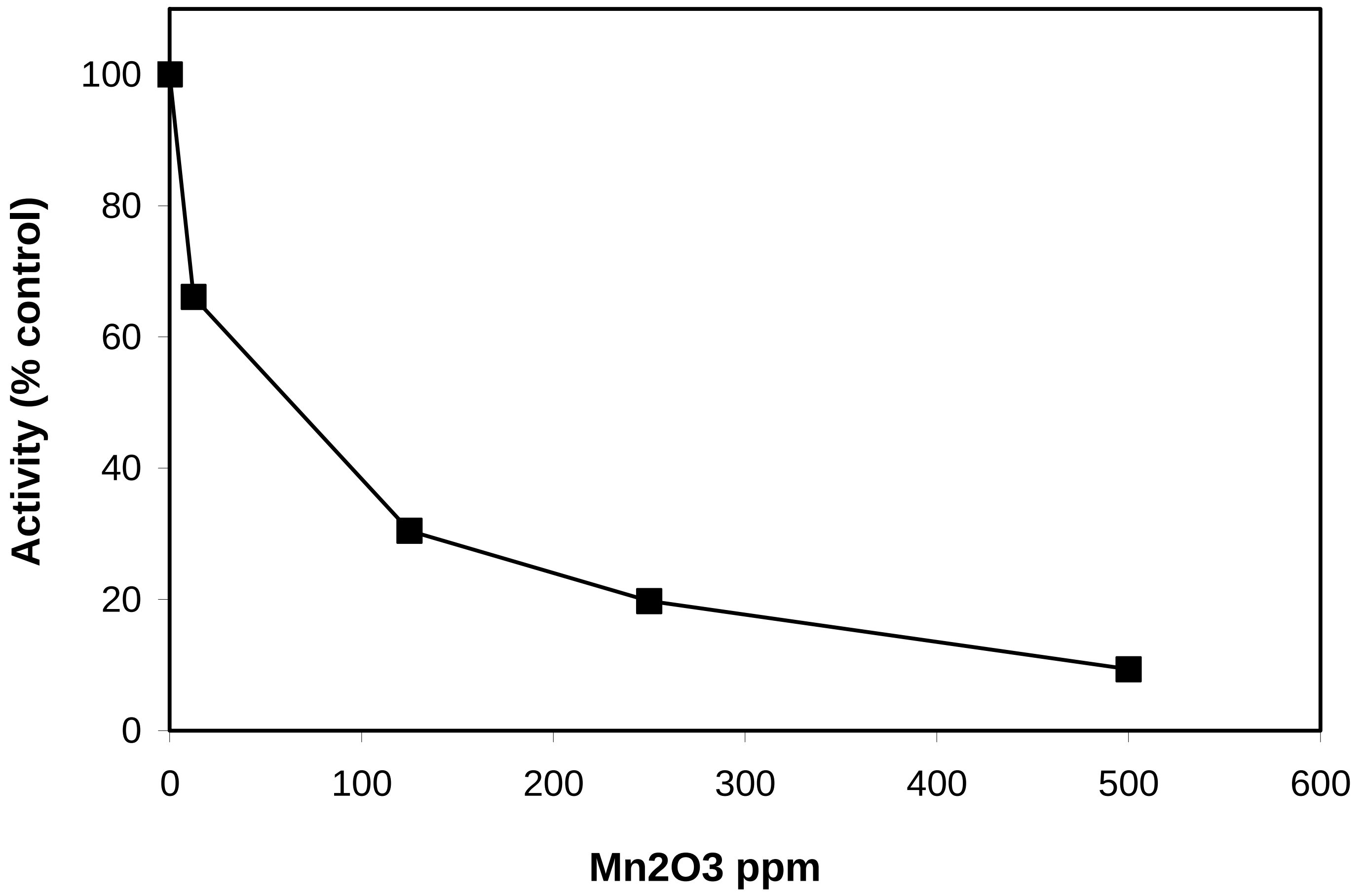
Results on CeO_2

Cerium oxide (MTI, “20 nm”). Example Live/Dead with Dispex



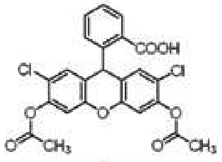
Results on Mn_2O_3

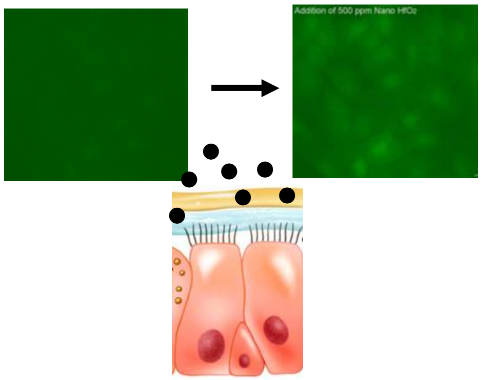
Manganese Oxide (SSNano, “40-60 nm”). Example Microtox with Dispex



Hypothesis ROS

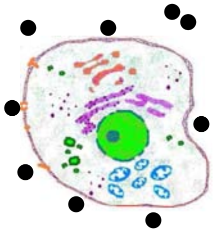
DCFH-DA



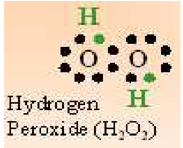


NP

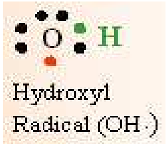
Cells

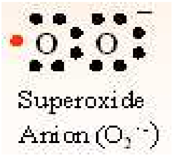


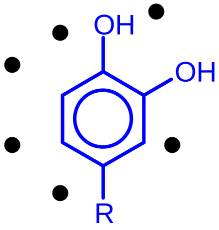
Enzymatic



ROS



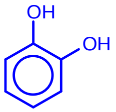


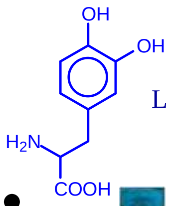


Chemical

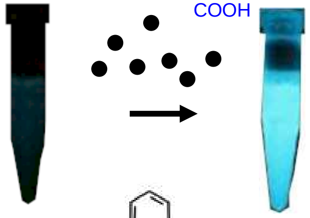
Biofluids

catechol

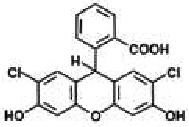




L Dopa

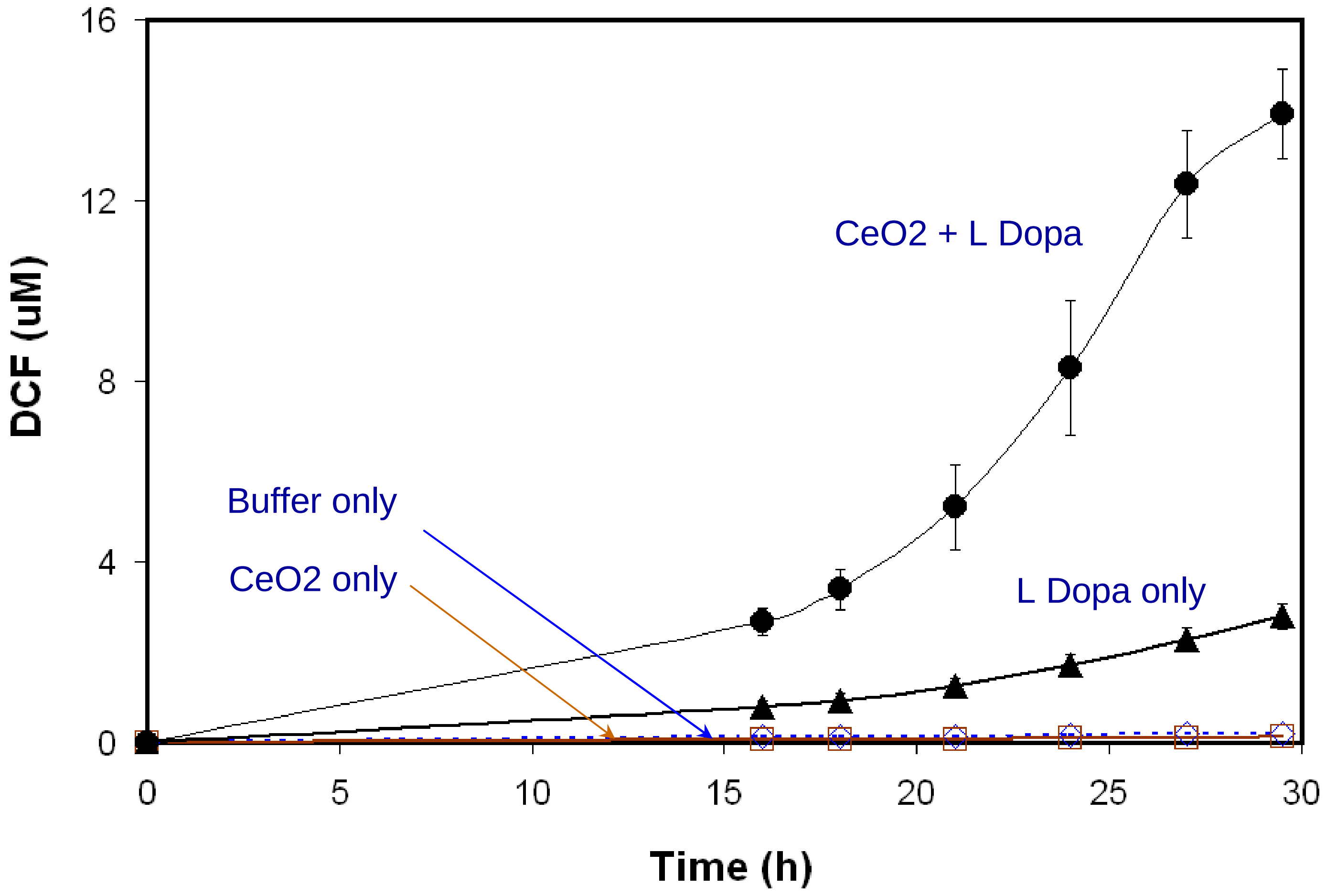


DCFH



Chemical Production ROS

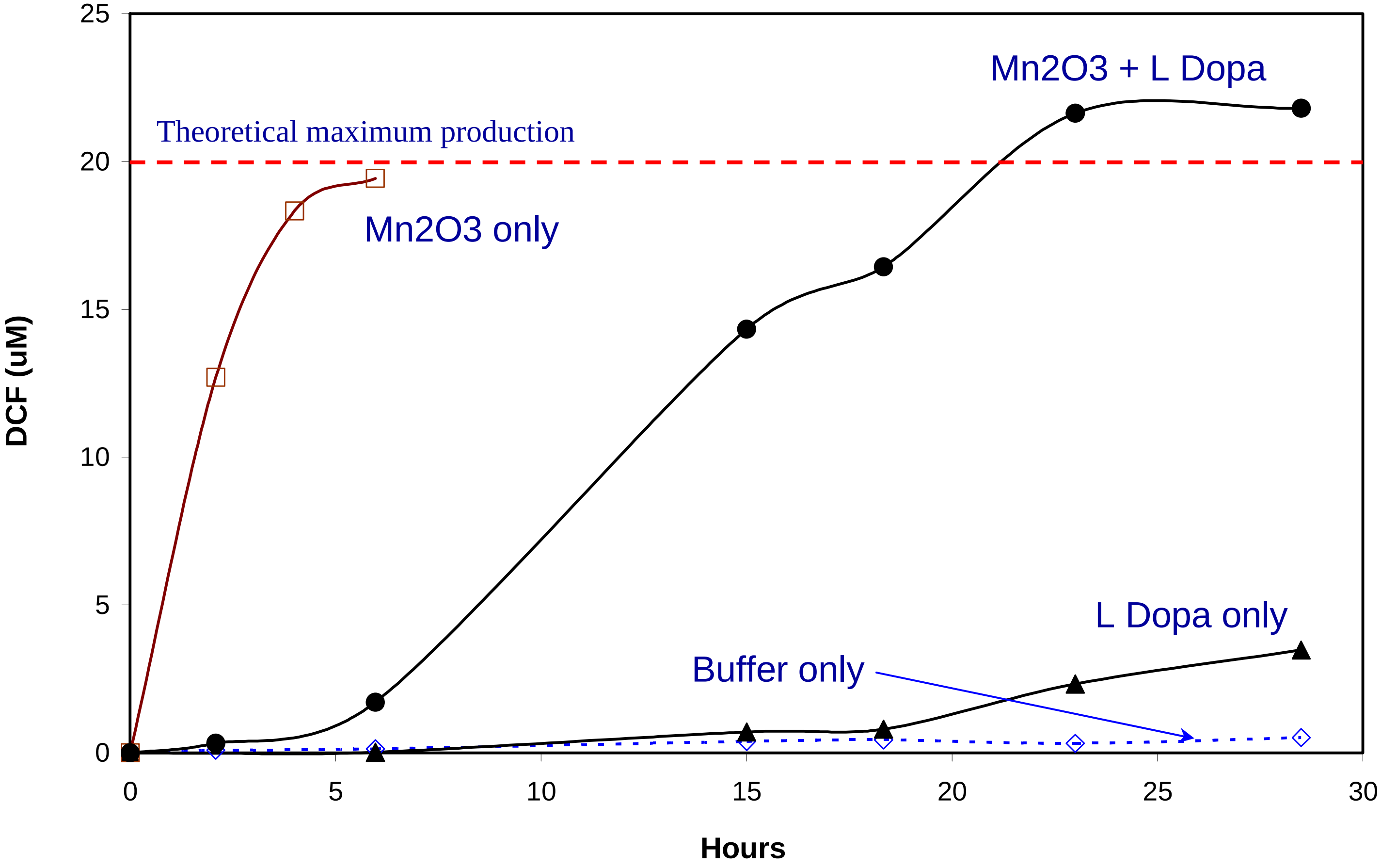
CeO2 (MTI, “20 nm”)



Results indicate that the oxidation of L Dopa by CeO2 NP produces ROS. Direct reaction of CeO2 with dissolved oxygen and water does not produce ROS

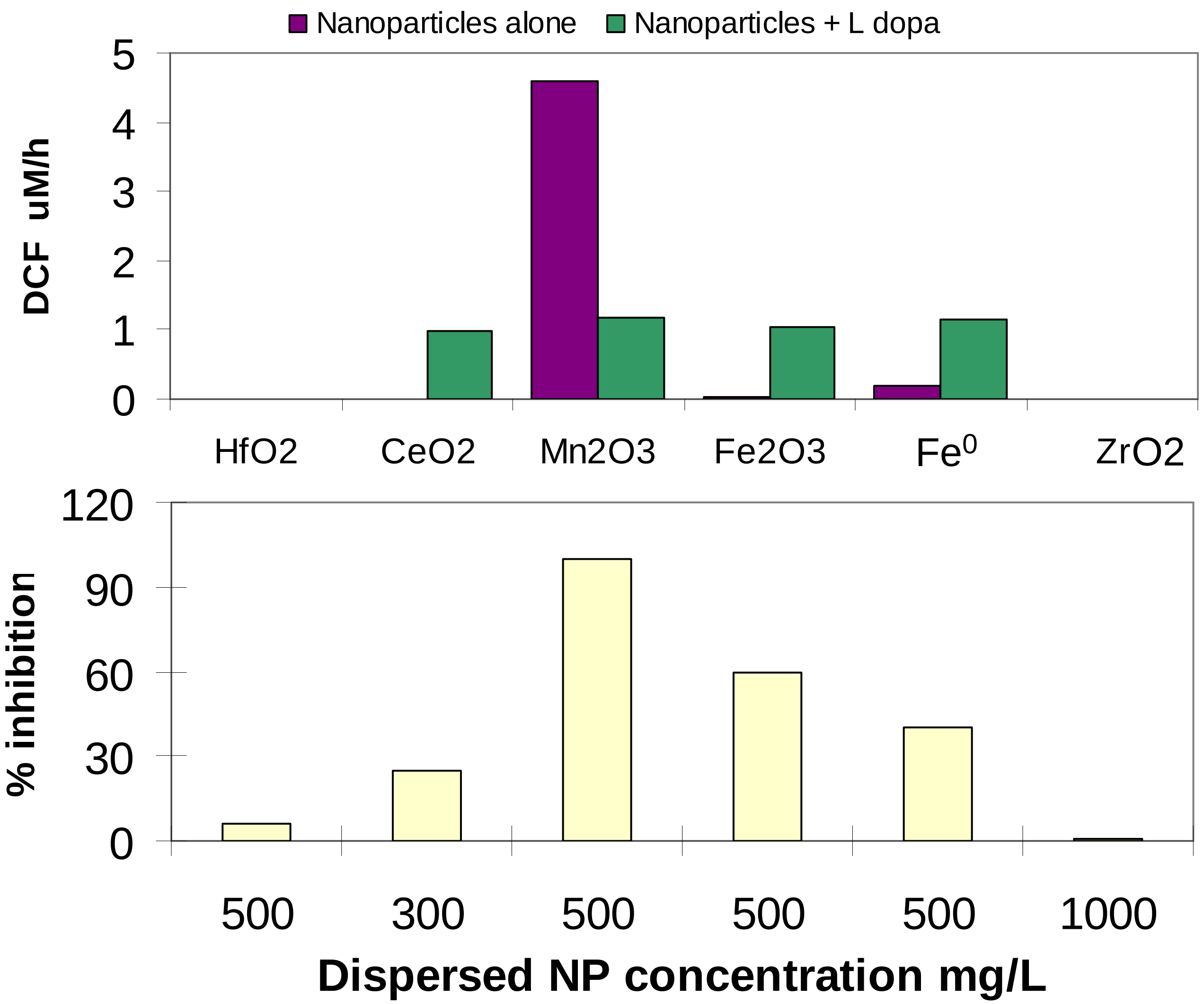
Chemical Production ROS

Mn2O3 SSNano “40-60 nm”).



Results indicate that the interaction of Mn2O3 NP with water and dissolved oxygen causes the formation of ROS. L Dopa inhibits the formation of ROS by Mn2O3

Correspondence ROS Versus Inhibition



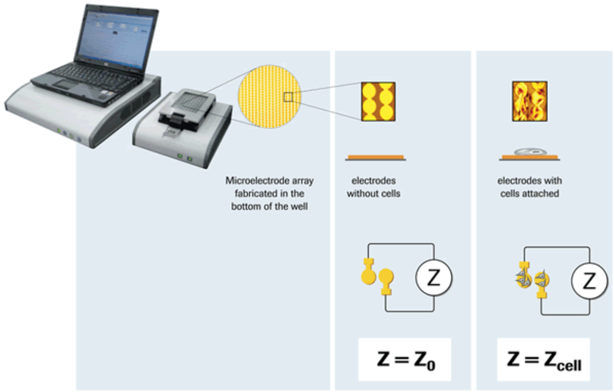
ROS assay

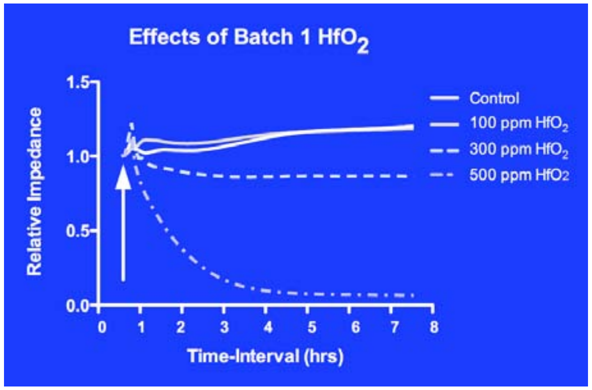
Microtox

Development New Techniques

New dye-free techniques that are less prone to interferences

- xCELLigence based on measuring impedance

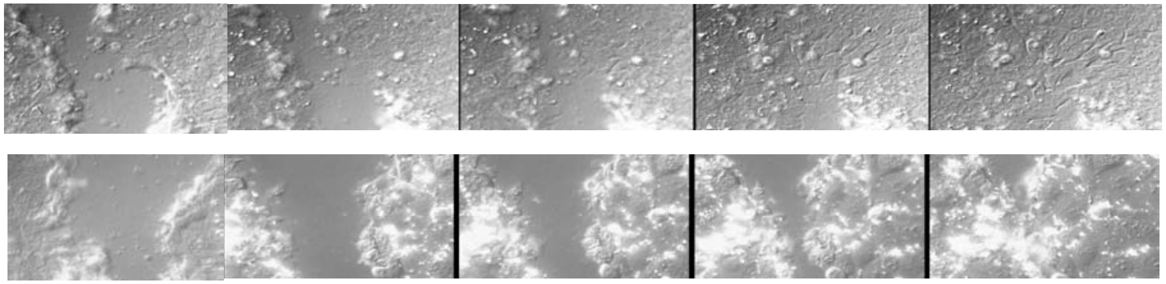




- Wound healing assay, based on time to close scrape wound

Time: 0 h 0.5 h 1.0 h 1.5 h 2.0 h

Batch 1 HfO2



Lung Cells

16HBE14o-

0 ppm

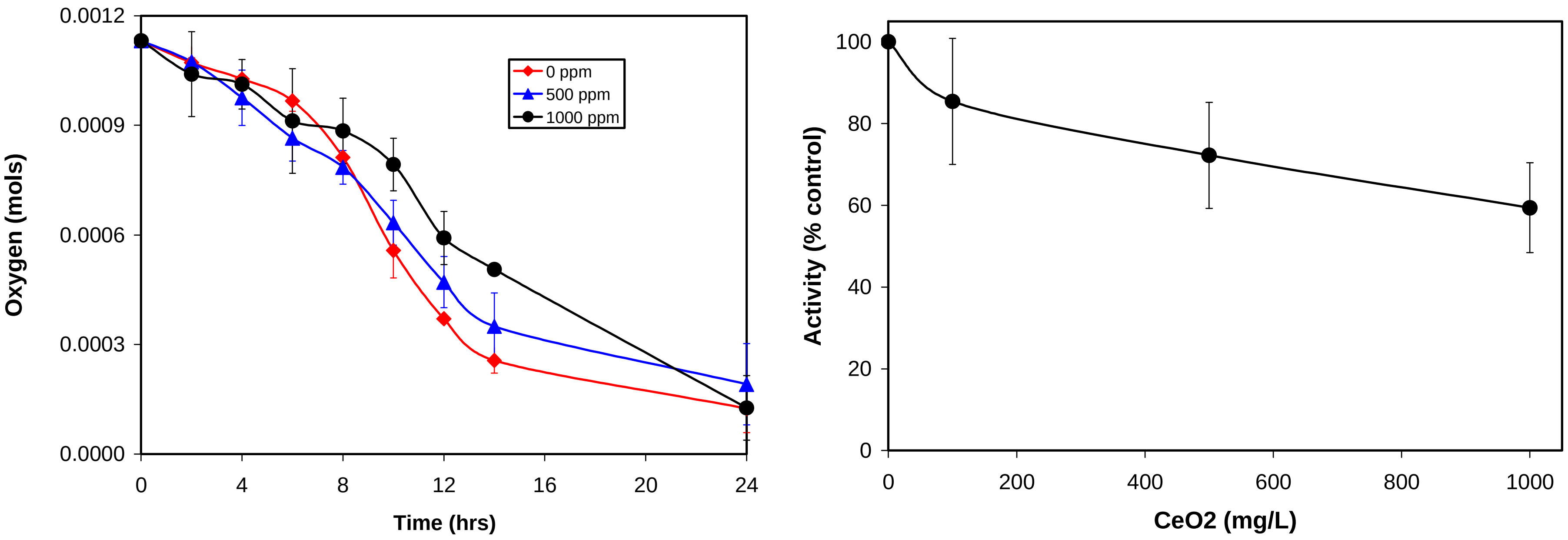
250 ppm

Development New Techniques

New dye-free techniques that are less prone to interferences (continued)

- O2 uptake assay for yeast and bacterial cells

Inhibition of Yeast, *Saccharomyces cerevisiae,* by CeO2



Preliminary Conclusions

- HfO2, ZrO2 and CeO2 NPs mild to no toxicity.

  Higher Toxicity of Batch 1 HfO2 may be due to chemical contamination (from synthesis)

	L/D 50% death	Microtox 50% inhib	Methanog 50% inhib
	--------------------	mg/L	-----------------------
HfO2*	**>2000**	**3000**	**>2500**
CeO2	**2500****	**>300****	**>1000**
ZrO2		**>1000****	

*batch3 **with dispersant

- NPs producing ROS directly in water most toxic. Chemical ROS production indicative of NP toxicity

Mn_2O_3	50% IC microtox = 70 mg/L
Fe_2O_3	50% IC microtox $\cong$ 500 mg/L
Fe^0	50% IC microtox $\cong$ 500 mg/L

Industrial Interactions and Technology Transfer

- **ISMI-Sematech (Steve Trammell, Laurie Beu)**
- **AMD (Reed Content)**
- **IBM (Arthur T. Fong)**
- **Intel (Steve W. Brown, Paul Zimmerman, Mansour Moinpour)**

Future Plans

Next Year Plans

- Fractionation of CeO2 for toxicity study size fractions
- Biochemical indicators of oxidative stress
- Complete development of new non-dye based techniques

Long-Term Plans

- Rapid screening protocols of for assessing NP toxicity
- Toxicity to organ models

Publications, Presentations

- **Brownbag presentation:** Nanoparticle Interaction with Biological Wastewater Treatment Processes, Water Sustainability Program, Phoenix, Arizona Jan 20th, 2010 at Arizona Cooperative Extension
- Sierra-Alvarez, R. 2009. Toxicity characterization of HfO_2 nanoparticles. SRC/Sematech Engineering Research Center for Environmentally Benign Semiconductor Manufacturing Teleseminar Series. August 6.
- Boitano, S. 2009. Measuring cytotoxicity of nanoparticles in human cells. SRC/Sematech Engineering Research Center for Environmentally Benign Semiconductor Manufacturing Teleseminar Series. Sept. 17.
- Ratner, B. 2009. Static SIMS: A Powerful Tool to Investigate Nanoparticles and Biology. SRC/Sematech Engineering Research Center for Environmentally Benign Semiconductor Manufacturing Teleseminar Series. May 14.