NANOPARTICLE SURFACE ACTIVITY:
UNDERSTANDING, MEASURING, AND INTEGRATING IT INTO DOSIMETRY

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Department of Environmental Health
The CHALLENGE

THE VIAL

THE FILTER
Outline

- **Surface in Inhalation Dosimetry**
  - Surface Area & Activity
  - Bench top Technologies and Options

- **Surface in ENM Exposure Assessment**
  - Gaps & Needs

- **Near Real-time monitoring of SAr and SAC**
Dose Metrics: A Historical Perspective

- MASS (ug/m3)
- RESPIRABLE FIBERS (f/m3)
- Viable & Total Microorganisms (#/m3)
Departing from Mass (OR NOT?)

Maynard & Kuempel 2005
SURFACE AREA METRIC

Maynard & Kuempel 2005
Surface Area as a Dose Metric

DOSE = f(SURFACE AREA, SURFACE ACTIVITY)
Physicochemical & Morphological Properties Influencing Toxicity

- Size Distribution
- Surface Area
- Surface Chemistry
- Surface Charge
- Bulk Chemical Composition
- Metals & Impurities
- Morphology
- Crystalinity
- Biopersistence
- Metal Leaching...

- Surfaces are NOT equal!
- Multiple parameters related to surface properties (SP)!
- How to measure these surface properties?
- How do these measures relate to biology/toxicology?

28 Properties in all (ICON 2007)
Next generation ENM: Safer-by design

Leaching of toxic ions\(^2\)  
Direct contact to toxic material\(^1\)  
Biologically "inert" nanothin SiO\(_2\) shell\(^3\)  
Preserve functional core-material\(^4,5\)

(1) Sotiriou et al., Curr Opin Chem Eng 2011, 1, 3 – 10
(2) Xia et al., ACS Nano 2011, 5, 1223 – 1235
(3) Napierska et al., Particle and Fibre Toxicology 2010, 7,39
(4) Teleki et al., Chem. Mater. 2009, 21, 2094–2100

Demokritou, ES Nano 2013
Impurities & Bioactivity

Doping of SiO$_2$ NPs with MeOx NP or Me$^{n+}$

CB +Fe$_2$O$_3$: Synergistic ROS generation

**Figure 2.** ROS concentrations in human lung epithelial cells after

Limbah et al ES&T 2007 41

**Guo et al PFT 2009**
Examples illustrate the importance of material composition, electronic structure, bonded surface species (e.g., metal-containing), surface coatings (active or passive), and solubility, including the contribution of surface species and coatings and interactions with other environmental factors.

Oxidative stress (OS) has been recognized in vivo and in vitro systems as one such major pathway and is being explored for ENM toxicity screening purposes (Nel et al. 2006; Xia et al. 2006; Borm et al. 2007; Ayres et al. 2008; Rogers et al. 2008; Bello et al. 2009; Lu et al. 2009; Meng et al. 2009).

<table>
<thead>
<tr>
<th><strong>System</strong></th>
<th><strong>Markers (of Oxidative Stress)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td>Cell free System</td>
</tr>
<tr>
<td></td>
<td>Measure ROS generation</td>
</tr>
<tr>
<td></td>
<td>DTT assay</td>
</tr>
<tr>
<td></td>
<td>DCFH-DA assay</td>
</tr>
<tr>
<td></td>
<td>EPR/ESR</td>
</tr>
<tr>
<td></td>
<td>Cellular System</td>
</tr>
<tr>
<td></td>
<td>Cell viability/Mitochondrial dysfunction</td>
</tr>
<tr>
<td></td>
<td>ROS – DCFH-DA assay</td>
</tr>
<tr>
<td></td>
<td>Activation of pro-inflammatory pathway</td>
</tr>
<tr>
<td></td>
<td>Inflammatory factors, cytokine production</td>
</tr>
<tr>
<td></td>
<td>Redox enzyme expression (HO-1, SOD)</td>
</tr>
<tr>
<td></td>
<td>DNA damage/cell mutagenesis/proliferation</td>
</tr>
<tr>
<td><strong>In vivo</strong></td>
<td>Inhalation</td>
</tr>
<tr>
<td></td>
<td>Similar to Cellular system</td>
</tr>
<tr>
<td></td>
<td>Luciferase Reporter, Cyt C</td>
</tr>
<tr>
<td></td>
<td>GSH depletion</td>
</tr>
<tr>
<td></td>
<td>Hematological, biochemical and pathologic change</td>
</tr>
</tbody>
</table>

ROS - Reactive oxygen species; DTT-Dithiothreitol; DCFH-DA-Dichlorofluorescin diacetate; HO-1; Heme oxygenase-1; SOD-superoxide dismutase; GSH-Glutathione; EPR-Electron paramagnetic resonance; ESR-Electron spin resonance
Approaches

Acellular

- **ESR/EPR**
  - Spin trapping with select agents (e.g. DMPO)

- **DTT**
  - Colorimetric

- **DCFH**
  - Fluorescence ($\text{RO}_2$, $\text{RO}$, $\text{OH}^-$, $\text{HOCl}$ and $\text{ONOO}$ but not $\text{O}_2^-$, and $\text{H}_2\text{O}_2$)

- **FRAS**
  - Human Serum - Colorimetric
ANALYTICAL APPROACH TO DETERMINE THE DEGREE OF OXIDATIVE STRESS EXERTED BY NANOPARTICLES IN HUMAN BLOOD SERUM BY FERRIC REDUCTION ACTIVITY OF SERUM (FRAS ASSAY)

Oxidatively Damaging Nanoparticles + Human Blood Serum (containing endogenous antioxidants e.g. VIT.E, VIT.C)

L-Ascorbic acid (Reduced form)

L-Dehydroascorbic acid (Oxidized form)

α-Tocopherol (Reduced form)

TPTZ-2,4,6-Tripyridyl-1,3,5azine

[Fe(III)(TPTZ)]^{3+} + ROOH

[Fe(II)(TPTZ)]^{2+}, \lambda_{max} = 593 \text{ nm}

RED

BLUE

Fe^{3+} + TPTZ

2,4,6-Tripyridyl-1,3,5azine
Efficacy of Simple Short-Term *in Vitro* Assays for Predicting the Potential of Metal Oxide Nanoparticles to Cause Pulmonary Inflammation

Senlin Lu,¹,² Rodger Duffin,¹ Craig Poland,¹ Paul Daly,¹ Fiona Murphy,¹ Ellen Drost,¹ William MacNee,¹ Vicki Stone,³ and Ken Donaldson¹

¹University of Edinburgh, Edinburgh, UK; ²School of Environmental and Chemical Engineering, Shanghai University, Shanghai, China; ³Napier University, Edinburgh, UK

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**Figure 6.** Relationship between free radical activity to cause inflammation *in vivo.*

**Figure 7.** DCFH fluorescence plotted against inflammatory cell viability as measured by PMN number for 0 cm²/mL surface area dose.

\[ y = 0.1098x + 1.0581 \quad R^2 = 0.752 \]

\[ y = 0.1311x + 0.8002 \quad R^2 = 0.6313 \]
Oxidative Stress vs. Inflammation

Rushton et al 2010

**DCFH**
- R² = 0.74

**ESR**
- R² = 0.79

**AMcell - ESR**
- R² = 0.95

**Luciferase Activity**
- R² = 0.88
FRAS vs ESR

Bello D, unpublished data

\[ y = 0.0273x + 67.895 \]

\[ R^2 = 0.0013 \]
FIGURE 1. Effect 0.01U of HRP on DCFH oxidation of blanks (no nanomaterials involved) under different conditions (sequence of events and dispersion conditions). The label on the X-axis reflects actual sequence of events. HRP is undoubtedly involved in DCFH oxidation and the magnitude of the effect spans approximately an order of magnitude compared to blanks without HRP, depending on the experimental conditions.
(A) (C)

ENMs

F_purified  F_Refined  F_Soot
MWCNT_J  MWCNT_L  MWCNT_M1
MWCNT_M  MWCNT_M  MWCNT_M
MWCNT_M  MWCNT_M  MWCNT_M
MWCNT_M  MWCNT_M  MWCNT_M
MWCNT_M  MWCNT_M  MWCNT_S
N110  N550  N990
nAg  nAl2O3  Silica
SWCNHs-ox  SWCNT_L  SWCNT_S
TiO2_mA  TiO2_mR  TiO2_nA  TiO2_nR

Spearman: 0.58
R^2 Linear: 0.32

Spearman: 0.62**
R^2 Linear: 0.68

Spearman: 0.58
R^2 Linear: 0.32

Spearman: 0.30
R^2 Linear: 0.11
Comparison of FRAS & DCFH for the 28 ENM

<table>
<thead>
<tr>
<th></th>
<th>Positive (10/28)</th>
<th>Negative (18/28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCFH</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>FRAS</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

N=28

Pal et al 2013 J Nano Research
### Comparison of intracellular oxidative stress elicited by ENMs (GSH assay) with acellular oxidative stress (via DCFH and FRAS)

<table>
<thead>
<tr>
<th>Nanomaterials Evaluated</th>
<th>Acellular assay responses</th>
<th>Cellular response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DCFH</td>
<td>FRAS</td>
</tr>
<tr>
<td>CB N-550</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>SWCNT_S</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>MWCNT_M1</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MWCNT_I</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>SWCNHs-ox</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>TiO$_2$-pA</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Silica</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(-) Indicates a response below the blank value (a negative response)

(+) Indicates a slightly positive ENM response relative to the overall response scale (between 10 and 50 percentile)

(+++) Indicates a highly positive ENM response relative to the overall response scale (between 75 and 95 percentile)

Pal et al 2014
J Nano Research
Table 2: Relationship between FRAS and DCFH responses and transition metal content in tested ENMs examined via Spearman Correlation Coefficients (r values) and Partial Correlation (SSA controlled).

<table>
<thead>
<tr>
<th>ENMs Set</th>
<th>Assay</th>
<th>Transition metal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fe</td>
</tr>
<tr>
<td>28 ENMs</td>
<td>FRAS</td>
<td>0.57**</td>
</tr>
<tr>
<td>(Spearman)</td>
<td>DCFH</td>
<td>0.50*</td>
</tr>
<tr>
<td>28 ENMs</td>
<td>FRAS</td>
<td>-----</td>
</tr>
<tr>
<td>(Partial)</td>
<td>DCFH</td>
<td>-----</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level

Pal et al J Nano Research 2013
Oxidative Stress vs. Inflammation

FRAS vs. Inflammation

PMN Number $\times 10^7/m^2$

sBOD (nmol TEUs/m$^2$)

Bello Unpublished data; PMN data: Alison Elder, U. Rochester
BOD (TEUs) = 0.75 * SSA (m²g⁻¹) + 0.418*Tₘₑ (ppm); R²=0.93

Bello, Hsieh et al 2010 Nanotoxicology

BOD ~ with SSA and the total content of Redox-active metals

Hsieh, Bello et al 2013
Distribution of FRAS BOD Values of 145 Tested ENMs

1. BOD is expressed as Trolox equivalent units. (TEUs, μmol L⁻¹).
2. Total antioxidant capacity of normal blood serum is 535 ± 15 μmol L⁻¹ TEUs.
3. 1000 TEUs BOD, near complete depletion of the antioxidants pool (5mg/mL).
4. 15 TEUs = The non-significant BOD
5. 25% of ENM <15 TEUs

Hsieh et al 2013 Small
Between-Class Variations in BOD

Hsieh, Bello et al, Small 2013
Within-Class Variation in BOD, CNTs

Hsieh, Bello et al. Small 2013

Number of ENMs within group

Error bars: 95% CI
Metal Oxides

Hsieh, Bello et al Small 2013

TiO$_2$

Error bars: 95% CI

Number of ENMs within group

BOD (TEUs; µmol L$^{-1}$)

BOD (TEUs; µmol L$^{-1}$)

0 500 1000 1500

Mn$_2$O$_3$ CuO NiO CoO Co$_3$O$_4$ ZnO Cu$_2$O Fe$_2$O$_3$ Fe$_3$O$_4$ NiO$_2$ CeO$_2$ TiO$_2$ ZrO$_2$ Al$_2$O$_3$ Min-U-Sil$_5$

hydrophilic fumed anatase rutile silane fumed unknown

C$_2$H$_5$OH

silver Zn Mo
Effect of CNT OD size on BOD

Surface Activity of narrow CNTs is much higher than for larger CNTs

Hsieh, Bello et al 2011 Nanotoxicology
Surface Activity vs. ENM Class

Hsieh, Bello et al Small 2013
Outline

◆ Surface in Inhalation Dosimetry
  o Surface Area & Activity
  o Bench top Technologies and Options

◆ Surface in ENM Exposure Assessment
  o Gaps & Needs

◆ Near Real-time monitoring of SAr and SAc
<table>
<thead>
<tr>
<th>Activity</th>
<th>Range of arithmetic means during activity</th>
<th>Number conc. by SMPS (particles/cm³)</th>
<th>Surface area concentration by LQ1-DC (µm²/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production—commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>1,661–39,087 (n = 12)</td>
<td>25–74 (n = 8)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>1,339–23,566 (n = 8)</td>
<td>21–69 (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Production—non-commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>3,887–21,441 (n = 7)</td>
<td>43–129 (n = 6)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>2,040–12,919 (n = 7)</td>
<td>35–93 (n = 3)</td>
<td></td>
</tr>
<tr>
<td>Down-stream use—commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>6,272–7,8376 (n = 9)</td>
<td>17–88 (n = 11)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>6,242–32,515 (n = 7)</td>
<td>18–51 (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Down-stream use—non-commercial scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nano-activity</td>
<td>234–380,494 (n = 57)</td>
<td>36–173 (n = 13)</td>
<td></td>
</tr>
<tr>
<td>No activity</td>
<td>199–34,507 (n = 55)</td>
<td>27–147 (n = 10)</td>
<td></td>
</tr>
</tbody>
</table>

Exposures to ENM by Task

Brouwer et al J Nanoparticle Res 2013, 15, 2090
Surface Area vs. Number Concentration

- <100 nm & ALVEOLAR
- >100 nm & TB
- 200-1000 nm & ACTIVE SA (LQ1-DC)

Brouwer et al Journal of Nanoparticle Research, 2013 15(11);
DOI:10.1007/s11051-013-2090-7

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ENM Exposures

- Gaseous Pollutants:
  - Ozone
t  - tVOC
  - CO/CO₂

- Particulate Matter (PM)

- IAQ:
  - Temp
  - RH

- Airborne PM

- Real-Time Measurements
  - FMPS
  - APS
  - CPC

- Integrated Samples

- Chemical Analysis:
  - Organic Carbon
  - Elemental Carbon
  - Elemental analysis by ICP-MS, total & water soluble
  - Semi-volatile organics (SVOC by GC-MS)

- Morphologic Analysis:
  - TEM/EDAX
  - SEM/EDAX

- Copier Filter

- Toner
Nanoparticle Emissions from Commercial Photocopiers

Bello et al Nanotoxicology 2012
Important Real-World Lessons

◆ NP Exposures are often to MIXTURES

◆ PCM Properties along the life cycle of NEPs may be DIFFERENT from input ENMs
  o Toxicological properties – likely DIFFERENT (by how much & what direction?)

◆ Multi-metric approach – necessary
  o Sufficient ?
  o Interpretation ?

◆ Exposure- dose equivalency for in vitro or in vivo work…
  o mass, number, surface area, elemental composition, ?,
Outline

- Current Metrology & Exposure Monitoring for ENM
- Surface Area
- Surface Activity – what does it tell us?
  - Benchtop Technologies and Options
  - Validity of the Concept
- Near Real-time monitoring of SAr and SAc

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Nanodevices
(FP7 project)
http://www.nano-device.eu/index.php?id=328

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of Device</th>
<th>WP</th>
<th>Measured physical metric</th>
<th>Type of nanoparticles</th>
<th>Particle size range</th>
<th>Ability to separate ENP from background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Low-cost total active surface area monitor</td>
<td>6</td>
<td>Total active surface area</td>
<td>Any</td>
<td>10 nm - 3 μm</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>NanoGuard</td>
<td>7</td>
<td>Number concentration, size distribution, morphology fingerprint</td>
<td>Any</td>
<td>&lt;20 nm - 450 nm</td>
<td>to be determined</td>
</tr>
<tr>
<td>3</td>
<td>Real-Time CNT Monitor</td>
<td>8</td>
<td>Number concentration</td>
<td>CNTs</td>
<td>all CNT sources</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Personal Nano-sampler</td>
<td>8</td>
<td>Mass concentration and size distribution of target ENP</td>
<td>Any</td>
<td>2 nm - 5 μm</td>
<td>No, only by further offline chemical analysis</td>
</tr>
<tr>
<td>5</td>
<td>Sampler/Preseparator for aerosol fraction deposited in the anterior nasal region</td>
<td>8</td>
<td>depending on the metrics of the used monitor</td>
<td>Compact isometric particles and agglomerates</td>
<td>5 nm - 400 nm</td>
<td>No, only by further offline chemical analysis</td>
</tr>
<tr>
<td>6</td>
<td>Sampler/Preseparator for aerosol fraction deposited in the gas exchange region</td>
<td>8</td>
<td>depending on the metrics of the used monitor</td>
<td>Compact isometric particles and agglomerates</td>
<td>20 nm - 5 μm</td>
<td>No, only by further offline chemical analysis</td>
</tr>
<tr>
<td>7</td>
<td>NanoDevice</td>
<td>9</td>
<td>Particle number and size</td>
<td>Any (no corrosive particles)</td>
<td>10 nm - 27 μm</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>MEMS-based airborne nanoparticle sensor</td>
<td>10</td>
<td>Mass concentration &amp; chemical composition</td>
<td>Any, but no CNTs</td>
<td>5 nm - 300 nm</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Catalytic Activity Aerosol Monitor (CAAM)</td>
<td>11</td>
<td>Catalytic activity concentration</td>
<td>Any with catalytic activity</td>
<td>No limitation in principle</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>CNT-detect</td>
<td>12</td>
<td>mass concentration</td>
<td>CNTs</td>
<td>all CNT sources</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Click for more information)

1. **Low-cost total active surface area monitor**
2. **NanoGuard**
3. **Real-Time CNT Monitor**
4. **Personal Nano-sampler**
5. **Sampler/Preseparator for aerosol fraction deposited in the anterior nasal region**
6. **Sampler/Preseparator for aerosol fraction deposited in the gas exchange region**
7. **NanoDevice**
8. **MEMS-based airborne nanoparticle sensor**
9. **Catalytic Activity Aerosol Monitor (CAAM)**
10. **CNT-detect**
Near-Real Time ROS Is Almost Here

Development and testing of an online method to measure ambient fine particulate Reactive Oxygen Species (ROS) based on the 2',7'-dichlorofluorescin (DCFH) assay

L. E. King and R. J. Weber

Fig. 4. Schematic of online PM_{2.5} ROS measurement approach using a mist chamber particle collection system and fluorometric probe.
Figure 6: Schematic of the PILS. A PM + steam mixture is cooled creating supersaturated conditions. Particles serve as condensation nuclei and grow into droplets large enough ($d_{ae} > 1 \mu m$) for collection at an impaction plate. DTT + F$^-$ enters above the plate and a continuous liquid flow is pumped downstream for electrochemical measurement of DTT consumption.
Direct On-filter FLD detection

- Ag NP
  - 0.3 ug/cm²
  - 0.8 ug/cm²
  - 6.3 ug/cm²
  - unexposed

- SiO₂ NP
  - 1.1 ug/cm²
  - 2.1 ug/cm²
  - 4.3 ug/cm²

Intensity vs. Wavelength, nm

Intesity vs. ENP concentration, µg/cm²

Silver NP

Silica NP

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Surface activity appears to integrate across multiple PCM parameters, including surface area.

Therefore, it is a critical parameter to capture, preferably in near-real time.

Additional parameter to SA.

The challenge— to develop the right technology.
My Collaborators

Prof. P. Demokritou, HSPH

Prof. E. Rogers
UMass Lowell

Prof. D. F. Schmidt
UMass Lowell

Prof. P. Gaines
UMass Lowell

Prof. J Mead,
UMass Lowell

Prof. B Wardle,
MIT

Prof. J Isaacs,
NEU

Dr. D. Brouwer,
TNO

Prof. Redlich,
Yale
Questions?
Monitoring NP Exposures, Instrumentation
Personal Samplers

- Personal size selective impactors
  - Naneum Aerosol PS 300
  - Several miniaturized impactors

- Quazi Personal Real-Time Monitors
  - Philips *NanoTracer* (10-300 nm, TNC, SD)
  - DiSCmini (Matter-Aerosol Inc.)
BOD Correlates Well with TELI in *E-Coli*

Table 2. Correlation Coefficients between TELI-Based Toxicity Endpoints with Other Toxicity EndPoints$^a$

<table>
<thead>
<tr>
<th>Correlation coefficient</th>
<th>$\text{TELI}_{\text{MAX}}$</th>
<th>$\text{Slope}_{\text{TELI}}$</th>
<th>$\text{TELI}_{\text{50}}$</th>
<th>$\text{NOTEL}_{\text{TELI}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTEL (mg/L)</td>
<td>$-0.51$</td>
<td>$-0.04$</td>
<td>$-0.20$</td>
<td>$0.40$</td>
</tr>
<tr>
<td></td>
<td>$(-0.4)$</td>
<td>$(-0.4)$</td>
<td>$(-0.2)$</td>
<td>$(0.2)$</td>
</tr>
<tr>
<td>EC50 (mg/L)</td>
<td>$-0.82$</td>
<td>$0.39$</td>
<td>$-0.61$</td>
<td>$0.78$</td>
</tr>
<tr>
<td></td>
<td>$(-1.0)$</td>
<td>$(0.4)$</td>
<td>$(-0.8)$</td>
<td>$(0.8)$</td>
</tr>
<tr>
<td>BOD (μmol/L)</td>
<td>$0.98$</td>
<td>$-0.63$</td>
<td>$0.80$</td>
<td>$-0.95$</td>
</tr>
<tr>
<td></td>
<td>$(1.0)$</td>
<td>$(0.4)$</td>
<td>$(0.8)$</td>
<td>$(0.8)$</td>
</tr>
</tbody>
</table>

$^a$The values shown are pearson product-moment correlation coefficients, the values inside the parentheses are spearman’s rank-order correlation coefficients.

Guo & Gu et al 2011 EST

“Toxicity Screening tests for new nanomaterials products are urgently needed. Whilst recognizing that oxidative stress potential may not be predictive of all possible adverse outcomes, tests based upon oxidative potential maybe an invaluable tool for initial screening and classification of the relative biohazard of such materials.”
INCREASED PRODUCTION OF FREE RADICALS, REACTIVE OXYGEN AND NITROGEN SPECIES (ROS, RNS)
e.g., •OH, •O₂, •ROO, •RO, H₂O₂, ONOO⁻

Key Metric: Biological Oxidative Stress

What SAMPLE TYPE do we use to check for this Oxidative Stress???
Exposure and Biokinetics of Nanosized Particles

Confirmed routes
Potential routes

Exposure Media
- Air, water, clothes
- Drug Delivery
- Air, water

Deposition
Injection

Uptake Pathways
- Skin

Translocation and Distribution
- Blood (platelets, monocytes, endothelial cells)
- Lymph
- GI-tract
- Liver
- Bone Marrow
- Other sites (e.g., muscle, placenta)
- Kidney
- Spleen
- Heart
- Sweat/exfoliation
- Urine
- Breast Milk
- Feces

Translocation rates are largely unknown!