TOXICITY OF NANOMATERIALS – DEVELOPMENT OF NEW THEORETICAL APPROACHES AT THE JSU INTERDISCIPLINARY NANOTOXICITY CENTER

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Acknowledgements

Dr. Al’ona Furmanchuk

Dr. Olexandr Isayev

Dr. Bakhtiyor Rasulev

Dr. Dinadayalane Tandabany

Agnieszka Gajewicz

Dr. Tomasz Puzyn
Interdisciplinary Nanotoxicity CREST Center – 2008

Ming Ju Huang and John Watts: “First-Principles Theoretical Description of Metal Clusters: Toward a Model of Metal Nanoparticles”

Tigran Shahbazyan and Serguei Goupalov: “Environment-Specific Issues in Nanoparticle Physics: Optical, Energy Transfer and Relaxation Processes”

Paresh Ray and Glake Hill: “Nanomaterial Based Surface Energy Probe (NSET) for Detection of Toxic Heavy Nano Metal Ions from Environmental Samples”

Huey-Min Hwang, Hongtao Yu and Paul Tchounwou: “Selecting Green Nanoparticles for Environmental Remidiation and Renewable Energy Applications”

Jerzy Leszczynski and Danuta Leszczynska: ”Modeling and prediction of toxicity and physical properties of nanomaterials”
## ICN Accomplishments (2008-2012)

<table>
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<tr>
<th>No. of Publications</th>
<th>No. of Book Chapters</th>
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<th>No. of Presentations</th>
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Non-governmental/Non-institutional awards include:
* Universal Technology Corporation
* United Technologies Research Center
* Johns Hopkins University
* Wright-Patterson Air Force Base (AFRL)
* Medipacs
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Current CREST Students

- Aida Demissie
- Anastasia Golius
- Bethlehem Negash
- Sharnek Walker
- Michael Cato
- Lucky Ahmed
- Kristen Lewis
- Patrina Thompson
- Marquita Watkins
- Kiara Walker
- Noel Matthews
- Brandy Vincent
- A.B.M. Zakaria
- Jean Negou
- Aminah Muhammad
- Guvanchmyrat Paytakov
- Christen Robinson
Governmental Nanotechnology Funding in Major Economies
There are now tens of thousands of papers written every year on nanoscience and nanotechnology topics. And it appears the growth trend continues unabated. The European Union produce the most nanoscience/nanotechnology publications while China shows the fastest growth.

Nanotechnology publications in the Science Citation Index (SCI) (*China includes Taiwan). Source: The National Nanotechnology Initiative: Second Assessment and Recommendations of the National Nanotechnology Advisory Panel. April 2008
Share of nanotechnology-related and all publications by country, 1991-2007

The Figure includes the top 25 countries by the share of nanotechnology-related publications 1991-2007.
Source: ISI Web of Knowledge, January 2008
Number of nanotechnology-related publications and patents

Source: ISI Web of Knowledge database, January 2008
Share of patents by nanotechnology sub-areas, 1995-2005

Number of Consumer Products that Include Nano-based Components

Source: Project on Emerging Nanotechnologies
Nano-Scares

Magic-Nano Controversy:
• The aerosol form of Magic Nano, a glass/ceramic sealant, has been recalled in Germany in 2006.
• Reason: Some customers were sickened by the aerosol and hospitalized?
• Is there nano in side Magic-Nano? Not known. Trade Secret!!!
• The Nanoethics Group, an nonpartisan research organization based in Santa Barbara, CA, said that the incident should be a "wake-up call" that the potential risks of nanotechnology are real and deserve more attention by both government and industry. "Historically, it takes something catastrophic, such as widespread injury from asbestos, for real action to be taken. This time, hopefully, we will be smarter than that and not wait for the other shoe to drop," said the group's research director, Patrick Lin.

Sunscreen Controversy:
• As per EPA findings, the nano-sized titanium dioxide particles found in sunscreens could cause brain damage in mice.
Donuts ...and Solar cells

How To Make a Solar Cell with Donuts and Tea
By Aaron Rowe  March 18, 2009 | 10:48 am | Categories: Uncategorized

Donuts and tea are the main ingredients in a MacGyver-style do-it-yourself solar cell, explained step-by-step in this video.

"It turns out these delicious little things contain everything we need to make a simple solar cell," said Blake Farrow, a Canadian scientist who filmed the video while visiting Prashant Kamat's lab at the University of Notre Dame.

Powdered sugar contains titanium dioxide nanoparticles,
Nano: How to Approach It

- Nanotechnology is a new science. Consequently, new knowledge is required to understand how novel materials may react with bio-molecules and participate in biological processes.

- Knowledge generation will be incremental and will take time but is worthwhile because it will lead to evidence-based decision making, safe design, and sustainability.

- New knowledge represents a multidisciplinary approach that demands a new ways of scientific collaboration.

- Recognition of the fact that we will have to make stepwise decisions as knowledge generation and data collection on commercial nano products proceed.

- Nano environmental awareness should be an integral part of design of new nanomaterials, and not as a post facto add-on or imposed cleanup cost.

Good:
- Nanorevolution
- Over 1000 products incorporate nanomaterials
- Projections: $3.1 trillion in global manufactured goods by 2015; 58,000 tons of nanomaterials by 2020

Bad:
- Nanorevolution
- Over 1000 products incorporate nanomaterials
- Projections: $3.1 trillion in global manufactured goods by 2015; 58,000 tons of nanomaterials by 2020

Ugly:
- Unpredictable and possibly severe health and environmental effects of some nanomaterials
Challenges of Nanomaterials: Are we on the way to comprehend their toxicity?
Challenges

• One needs to be able to predict the toxic effects of nanomaterials
  ... remembering toxicology is complex

• One has to bring more chemistry into predictive toxicology

• Efficient, predictive computational chemistry methods should be developed and applied

• Interactions between experimentalists are crucial
Postulated mechanisms of NPs’ toxicity

- Effects on macromolecules
- Effects on gene expression
- Effects on enzyme activity
- Effects on membranes

Chemical Inventory and Toxicological Testing in USA

• In USA, National Toxicology Program (NTP) is responsible to evaluate chemical agents having public health concern.

• Other agencies e.g. Environmental Protection Agency (EPA) and National Institute of Occupational Safety and Health (NIOSH) also have an important role.

• There are about 80000 chemicals currently registered in USA for commercial use.

• Only 350 have undergone long-term and 70 short-term testing by NTP.

• Testing of each bioassay costs $2-4 million and over 3 years to complete test.

• Thus, in total about $160-320 billion and 240 thousand years total time will be needed to test chemicals currently in use.
Why Computational Approaches are Vital?

• Solving problems
• Making predictions directly
• Linking structure to properties and activities
• Not requiring animal testing
• Providing various levels of accuracy
• Allowing to merge various approaches
• Being fast and inexpensive
Computational approaches

• Molecular Modeling
• Quantum-Chemical Approaches
• QSARs: Quantitative Structure-Activity Relationships

Physical Properties
Toxicity
Environmental Distribution

Biokinetic Parameters
Basic concept of QSAR modeling

Endpoint (experimentally measured)

\[ y = f(X) \]

(eg. \( y = b_0 + b_1x_1 + b_2x_2 \))

QSAR model

Structural descriptors

- Linear Regression (LR)
- Multiple Linear Regression (MLR)
- Partial Least Squares (PLS)
- Artificial Neural Networks (ANN)
- …

- Dipole moment
- Polarizability
- HOMO, LUMO
- Topological indexes
- Number of specific atoms/groups
- …

- Activity (EC\(_{50}\))
- Phys/Chem property (K\(_{OW}\), t\(_{1/2}\))
- Retention parameters (t\(_R\))
- Toxicity (LD\(_{50}\), LC\(_{50}\))
- …
The most challenging problems for Nano-QSAR

1. Scarce and/or inconsistent empirical data and lack of conceptual frameworks for grouping NPs according to modes of toxicity and phys/chem properties

2. Lack of appropriate descriptors able to express specificity of nano-structure

3. Limited knowledge on the interactions between NPs and dispersants as well as biological systems (DNA, proteins, membranes etc.)

4. Lack of rational structure-activity modeling procedures, taking into account size-dependent differences between the bulk and nanostructure
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Experimentalists vs. QSAR modelers

Nanoparticles

Endpoints

Data for QSAR

Nanoparticles

Endpoints

Data from experiments
Existing databases

OECD Database on Research into the Safety of Manufactured Nanomaterials

Human Health and Environmental Safety Research

OECD Database on Research into Safety of Manufactured Nanomaterials is a global resource which details research projects that address environmental, human health and safety issues of manufactured nanomaterials. This database helps identify research gaps and assists researchers in future collaborative efforts. The database also assists the projects of the OECD's Working Party on Manufactured Nanomaterials (WPMN) as a resource of research information.

This database builds on the database of the Woodrow Wilson International Center for Scholars: Nanotechnology Health and Environmental Implications: An Inventory of Current Research.
JRC NANOHub database
(http://www.napira.eu)
JRC NANOhub database
(http://www.napira.eu)
JRC NANOHub database
(http://www.napira.eu)

NANOHub installations available

Projects

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OECD-WPMN Projects

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<td>OECD-WPMN SG7</td>
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<td>OECD-WPMN Silicon Dioxide</td>
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<td>OECD-WPMN Silver</td>
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<td>OECD-WPMN Titanium Dioxide</td>
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<td>OECD-WPMN Zinc Oxide</td>
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</table>
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Specific structural features of NPs

Toxicity of NPs can be related to:

- size
- size distribution
- agglomeration state
- shape
- porosity
- surface area
- chemical composition
- structure-dependent electronic configuration
- surface chemistry
- surface charge
- crystal structure

Oberdörster et al. *Particle and Fibre Toxicol.* 2: 8.
Calculating 3D descriptors based on the whole system


Calculations performed at the Density Functional Theory (DFT) level: B3LYP/6-31G(d)

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Experimental techniques that can be used to obtain nano-descriptors


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<td>Volume</td>
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<td>Area</td>
<td>EM, AFM</td>
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<tr>
<td>Surface charge</td>
<td>z-Potential, electrophoretic mobility</td>
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<td>XRD, TEM-XRD</td>
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<td>FFF-ICP-MS</td>
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<td>Aggregation state</td>
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<td>Hydrophobicity</td>
<td>Liquid-liquid extraction chromatography</td>
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<td>Hydrodynamic diameter</td>
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<td>Equivalent pore size diameter</td>
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**Abbreviations:**

- EM - electronic microscopy,
- AFM - atomic force microscopy,
- FFF - field flow filtration,
- DLS - dynamic light scattering,
- LC - liquid chromatography,
- XRD - X-ray diffraction,
- TEM - transmission electron microscopy,
- ICP-MS - inductively coupled plasma mass spectrometry,
- ICP-OES - inductively coupled plasma emission spectroscopy,
- EDX - energy dispersive X-ray spectrometry,
- ESEM - environmental scanning electron microscopy.
The most challenging problems for Nano-QSAR

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Agglomeration and aggregation of NPs

Formation of protein coronas

Optimized Structures of G-Au$_n$ and GC-Au$_n$


NBO charges for selected atoms are given in green color while selected gold atoms and base distances are in Å.
Interactions of G, GC and AT with C₆₀ and SWNTs

M. Shukla, J. Leszczynski, (2009), CPL, 469, 27; ibid (2010), 493, 126; ibid (2010), 496, 130
Collaboration within „classic“ QSAR studies

QSAR

Experimental toxicology
What we need to develop Nano-QSARs?

Experimental structure characterization

Nano-QSAR

Experimental toxicology
The most challenging problems for Nano-QSAR

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Data for „classic” QSAR and Nano-QSAR studies

„Classic” QSAR

Nano-QSAR
Size-dependence of QM properties/descriptors


**Scheme A:** GAP, HOMO, LUMO, hardness, softness, electrophilicity
Size-dependence of QM properties/descriptors \cite{2}


**Scheme B:** HOF, total energy, electronic energy, SAS, dipole moment
Preliminary QSAR model predicting cytotoxicity of nano-sized oxides particles to *E. coli* [1]

Using nano-QSAR to predict the cytotoxicity of metal oxide nanoparticles

Tomasz Puzyn¹, Bakhtiyor Rasulev¹, Agnieszka Gajewicz¹,², Xiaoke Hu³, Thabitha P. Dasari³, Andrea Michalkova¹, Huey-Min Hwang³, Andrey Toropov⁴, Danuta Leszczynska⁵ and Jerzy Leszczynski¹,*

It is expected that the number and variety of engineered nanoparticles will increase rapidly over the next few years¹, and there is a need for new methods to quickly test the potential toxicity of these materials². Because experimental evaluation of the safety of chemicals is expensive and time-consuming, computational methods have been found to be efficient alternatives for predicting the potential toxicity and environmental impact of new nanomaterials before mass production. Here, we show that the quantitative structure-activity relationship (QSAR) method commonly used to predict the physicochemical properties of chemical compounds can be applied to predict the toxicity of various metal oxides. Based on experimental testing, we have developed a model to describe the cytotoxicity of 17 different types of metal oxide nanoparticles to bacteria *Escherichia coli*. The model reliably predicts the toxicity of all considered compounds, and the methodology is expected to provide guidance for the future design of safe nanomaterials.

between the structures of 17 metal oxides and their cytotoxicity to *E. coli* cells. Based on this model and experimental data⁴, we have hypothesized the most probable mechanism for the cytotoxicity of these nanoparticles. We investigated this cytotoxicity in bacteria, because although they are single-celled organisms, they can be used to evaluate the cytotoxicity of higher organisms. Indeed, because of their metabolic versatility, bacteria are considered an excellent ecological indicator for evaluating the persistence and impact of xenobiotic chemicals on environmental health and ultimately human health⁵. Furthermore, differences in the activity of individual oxides can be useful in dental applications, where they are used as antibacterial agents. Also, because bacteria, as decomposers, play an important role in natural ecosystems, the uncontrolled emission of highly bacteriotoxic substances may disrupt the natural balance and create unpredictable effects in the environment⁶.

The nano-QSAR model was based on experimental data gathered in our laboratory for 17 metal oxide nanoparticles. The number of
Preliminary QSAR model predicting cytotoxicity of nano-sized oxides particles to *E. coli* \(^{[2]}\)


- 17 oxides NPs: ZnO, CuO, V\(_2\)O\(_3\), Y\(_2\)O\(_3\), Bi\(_2\)O\(_3\), In\(_2\)O\(_3\), Sb\(_2\)O\(_3\), Al\(_2\)O\(_3\), Fe\(_2\)O\(_3\), SiO\(_2\), ZrO\(_2\), SnO\(_2\), TiO\(_2\), CoO, NiO, Cr\(_2\)O\(_3\), La\(_2\)O\(_3\)


- 12 electronic descriptors calculated at the semi-empirical PM6 level
Preliminary QSAR model predicting cytotoxicity of nano-sized oxides particles to \textit{E. coli} [3]


\[
\log\left(\frac{1}{\mathcal{L}C_{50}}\right) = 2.59(\pm 0.07) - 0.50(\pm 0.07) \cdot \Delta H_{\text{Me}^+}
\]

\( n = 10, \ n_{\text{test}} = 7, \)
\( F = 45.4, \ p < 0.001, \)
\( R^2 = 0.85, \ Q^2_{\text{CVLOO}} = 0.77, \)
\( Q^2_{\text{test}} = 0.83, \)
\( \text{RMSEC} = 0.20, \)
\( \text{RMSECV} = 0.24, \)
\( \text{RMSEP} = 0.19 \)
Postulated mechanisms of NPs’ toxicity

- Effects on macro-molecules
- Effects on membranes
- Effects on gene expression
- Effects on enzyme activity
- Physical effects of size and shape
- Inflammatory response
- Surface reactivity
- Release of NPs constituents
- Vector for other contaminants
- Other contaminants

The dose makes the poison

The detailed characterization of the materials is essential in all areas of nanotoxicology.

Fish, worms, rodents, algae, bacteria and cells. Carbon nanotubes, metal oxides and quantum dots. Choose a model system from the first list and a nanomaterial from the second, and chances are that you will be able to find two or more toxicity studies that report slightly different conclusions about the impact of the latter on the former. Twenty years of research has confirmed that nanoscale materials can display unexpected and unusual toxicity, but just how much have we learnt about the interactions between engineered nanomaterials and humans, animals and the environment?

The Society of Toxicology defines toxicology as "the study of the adverse effects of chemical, physical and biological agents on people, animals and the environment". One characteristic of nanotoxicology is that materials that are not harmful in their bulk form may well be toxic on the nanoscale. Bulk gold, for example, is normally inert but gold nanoparticles are anything but inert, which is why they are useful for applications such as medical imaging and drug delivery. However, nanoparticles are also more likely to react with cells and various biological components such as proteins, and to travel through organisms, which increases their chances of entering various organs and activating inflammatory and immunological responses.

In a typical toxicity test, cells or organisms are subjected to a dose of chemicals, and the response is measured over a period of time; the dose–response relationships obtained in these experiments are important because they are used for determining appropriate dosages for drugs and acceptable limits for exposure to pollutants. However, unlike the soluble chemicals tested in traditional toxicity studies, nanoparticles have shapes and surface areas, and they can diffuse, aggregate/agglomerate and sediment according to their size, density and physical and chemical properties in solution. This means that traditional in vitro assays may misrepresent the response and cellular-uptake data for nanoparticles, making the test results less comparable across particle types than for soluble chemicals. On page 385 of this issue Xia and co-workers show that sedimentation of nanoparticles can influence how many nanoparticles are taken up by cells in an in vitro assay, and on page 332, Lison and Huaux discuss the different options for defining the relevant cellular dose for such tests.

There are opportunities for computational scientists to work with toxicologists to design new assays.

Another issue in nanotoxicology is the impact of nanomaterials on the environment. Many toxicity studies, until now, have been done at much higher doses than is realistic and they may not fully reflect Paracelsus's observation of "the dose makes the poison" — toxic substances are harmless in small doses and harmless substances are poisonous when over-consumed. Quantifying real-life occupational exposures and emissions of nanoparticles into the environment is a challenge; modelling studies that consider various exposure scenarios based on the life cycle of the nanomaterials and products that contain them have been presented, but to improve these models we require data on the industrial production of nanomaterials, the amounts released at different stages of the life cycle of the materials, and the form in which they are released.

The chemical and physical properties of nanoparticles have a strong influence on the way in which they interact with biological components or the environment at large, and also on the way they move, accumulate and clear in the body. For example, nanoparticles acquire a "corona" of proteins when exposed to biological fluids, and this layer is thought to influence the way this, and the effect of the nanoparticle. It has also been shown that the shear layers of nanoparticles can induce proteins to unfold, leading to an inflammatory response. Similarly, nanoparticles are coated with natural organic matter when they enter water, soil or sediment environments and this layer influences their reactivity, biodegradability and other transformations in the environment. These dynamic interactions add complexity to the challenge of determining the biological outcome of nanoparticles.

Studying the influence of the various properties of nanomaterials, the dose, the exposure route and time, and identifying the right model systems is expensive and time consuming. High-throughput and computational approaches are on the horizon to rapidly screen and prioritize nanomaterials for toxicological tests and to develop causal relationships between material properties and biological behaviours. Researchers have shown, for example, that the quantitative structure–activity relationship (a statistical model traditionally applied to chemicals) can predict the cytotoxicity of a small set of metal oxide nanoparticles; there are also opportunities for computational scientists to develop appropriate structural parameters for describing nanomaterials and to work with toxicologists to design new assays.

For the field to progress, it is necessary for all papers to report detailed characterization of the materials used so that data from the toxicity studies can be properly interpreted, reproduced and compared by others. And the big challenges in the coming years are to understand how physical and chemical properties of nanomaterials govern their interactions and responses, and to inform the public on the benefits and risks associated with the use of nanomaterials.

References
2. www.nature.com/nano/feature/nanotoxicology
Thank you for your attention!