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

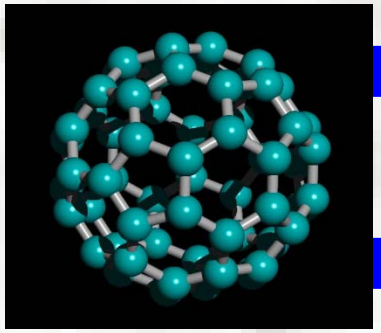
Dr. Tomasz Puzyn

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"



Modeling

Experiment

Structural, Physical and Quantum-Chemical Properties

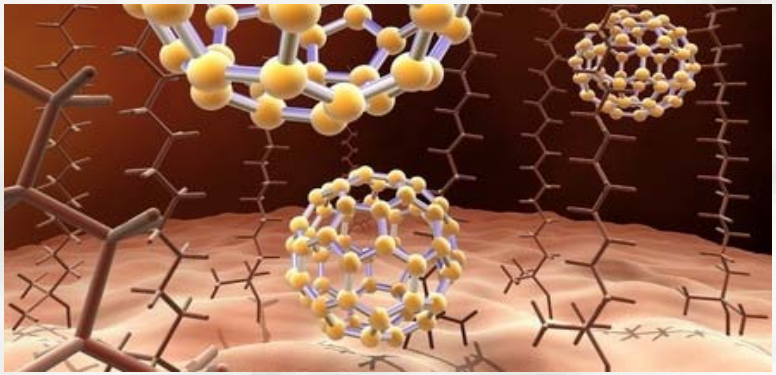
***In vitro* data**

QSAR model

Predicting the activity for untested compounds

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)

No. of Publications	No. of Book Chapters	No. of Students	No. of Presentations	Amount of Funding	No. of Grants	No. of Non-governmental/Non- institutional Awards	Amount of Non-governmental/ Non-institutional Awards	No. of Students Graduated
Total: 251	**17**	**120**	**219**	**22,701,829**	**58**	**11**	**619,999**	**13**
2008: 50	3	32	60	3,266,738	10	1	25,000	3
2009: 56	6	34	63	4,801,016	11	2	84,999	5
2010: 72	3	28	41	6,920,483	14	3	225,000	2
2011-12: 73	7	26	47	7,713,592	23	5	285,000	3

Non-governmental/Non-institutional awards include:

*Universal Technology Corporation
*United Technologies Research Center
*Johns Hopkins University
*Wright-Patterson Air Force Base (AFRL)
* Medipacs

American Chemical Society, Directory of Graduate Research

Publications per Faculty per Year

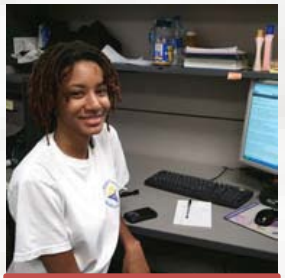
School	No. Faculty	2009	2010
JSU	**18**	**5.8**	**6.8**
Miss. State	20	1.2	1.4
Univ. Southern Miss.	13	5.8	3.2
Univ. Mississippi	14	1.0	1.4
Cal State LA	16	8.6	3.4
Cal State Fullerton	17	1.1	1.0
UT San Antonio	17	2.0	2.5
Howard	20	3.2	1.5
Clark Atlanta	9	7.4	2.3
Louisiana Tech	11	2.6	0.4
LSU	39	4.3	2.7
Univ. Alabama	26	3.5	4.2
Univ. Memphis	21	2.1	1.9
Univ. Arkansas	21	1.6	2.2
Univ. Tennessee	30	5.9	4.7
Univ. Kentucky	33	4.0	4.2
Univ. Georgia	29	7.0	7.7
Florida State	32	4.0	4.6
Auburn Univ.	24	2.1	2.2
Univ. South Carolina	29	4.6	4.2
Vanderbilt	31	7.1	6.1
Duke	23	5.6	5.3

Current CREST Students


Aida Demissie


Anastasia Golius

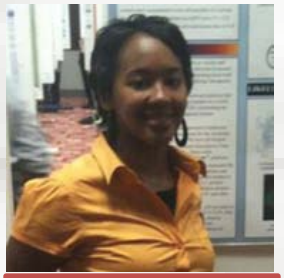

Bethlehem Negash


Sharnek Walker


Aminah Muhammad

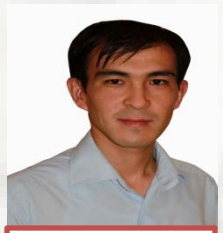

Michael Cato


Lucky Ahmed

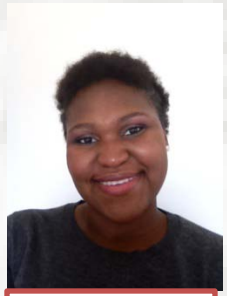

Kristen Lewis


Patrina Thompson


Marquita Watkins


Guvanchmyrat Paytakov


Christen Robinson


Kiara Walker

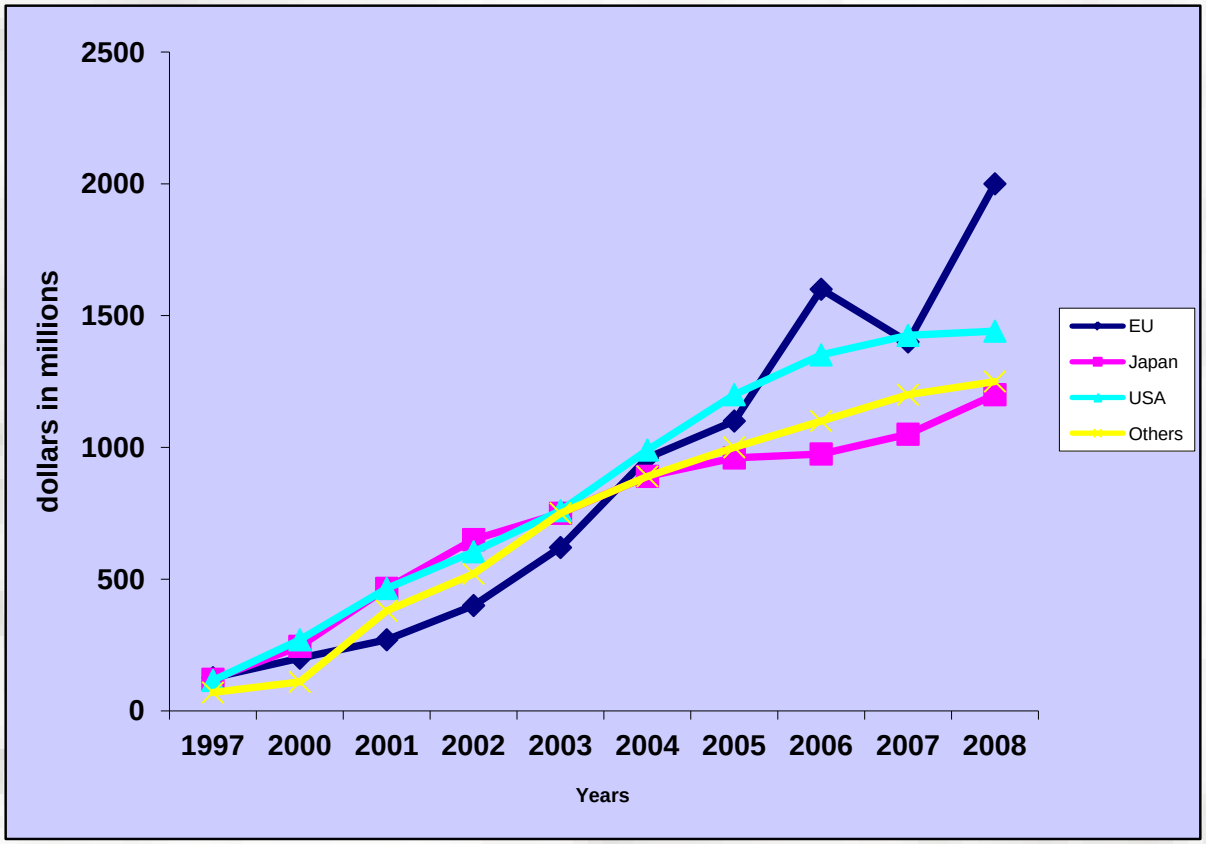

Noel Matthews


Brandy Vincent


A.B.M. Zakaria

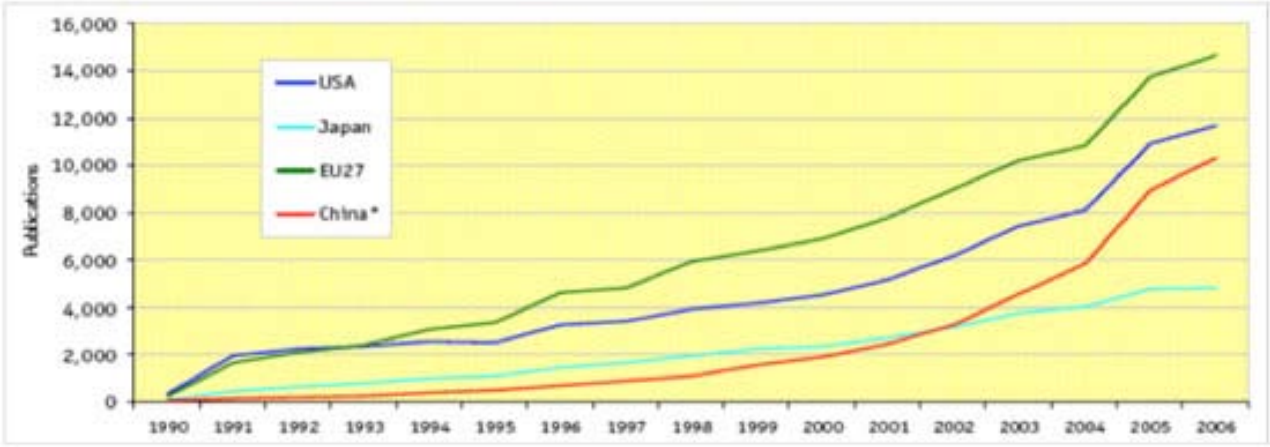

Jean Negou

Governmental Nanotechnology Funding in Major Economies



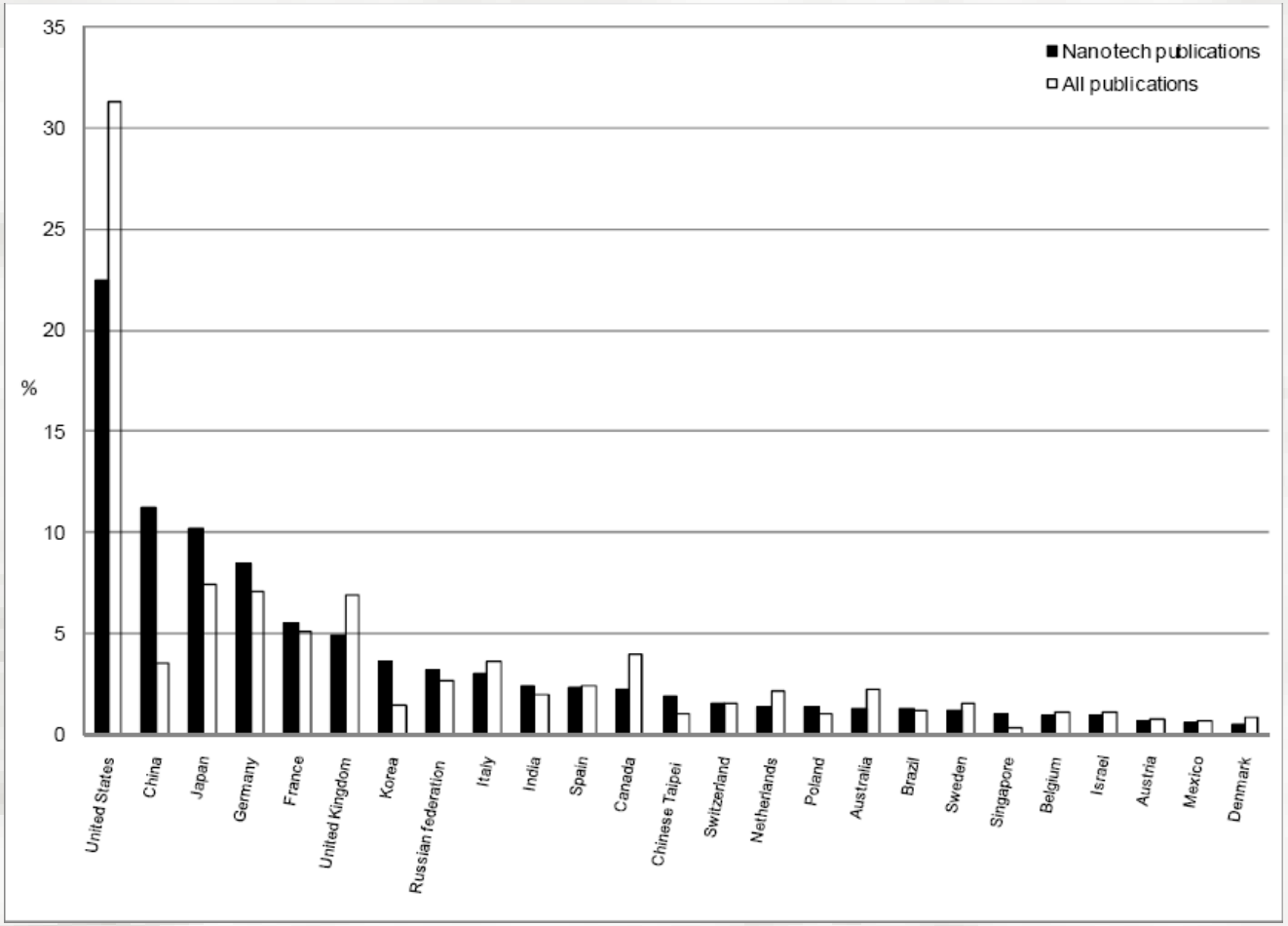
Scientific Papers

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.



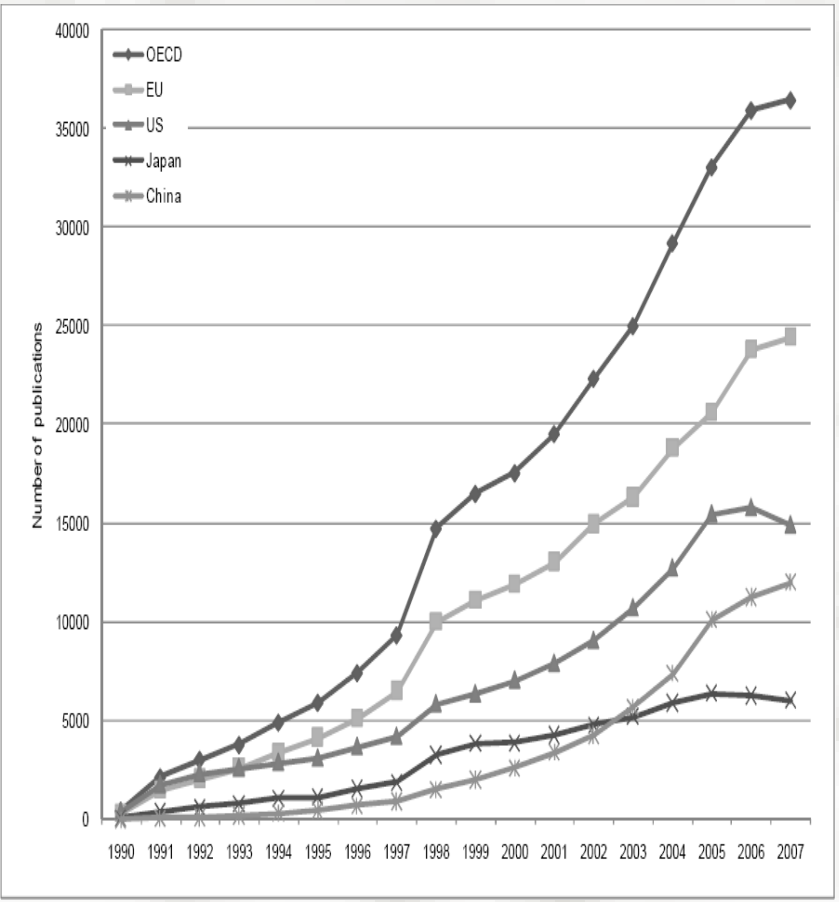
*Nanotechnology publications in the Science Citation Index (SCI) (*China includes Taiwan). Source: The National Nanotechnology Initiative: Second Assessment and Recommendations of the National Nanotechnology Advisory Panel. April 2008*

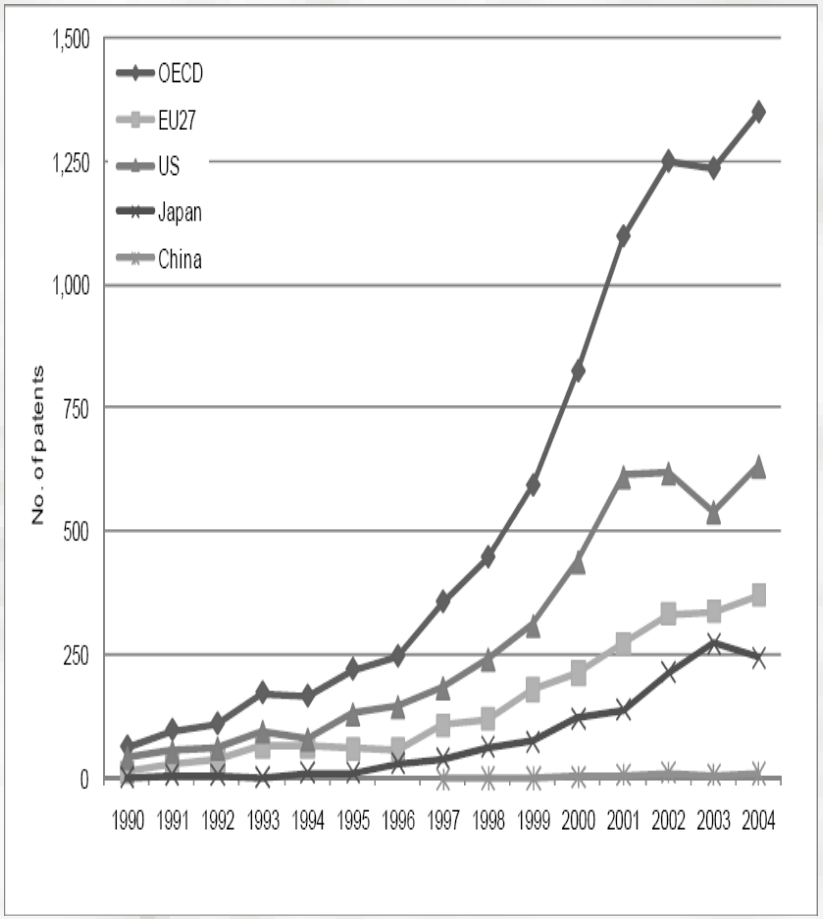
Share of nanotechnology-related and all publications by country, 1991-2007



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

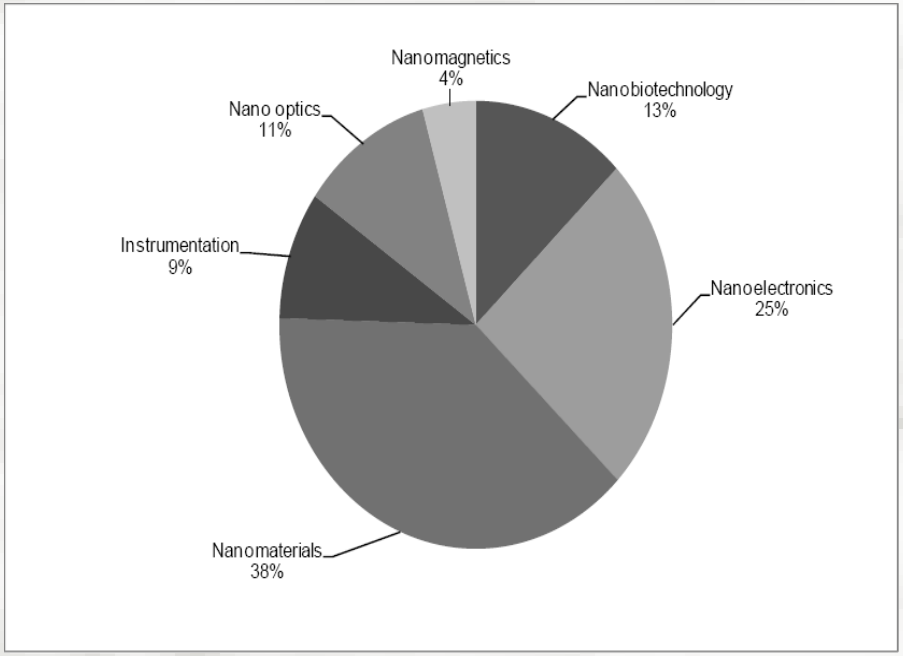
Number of nanotechnology-related publications and patents

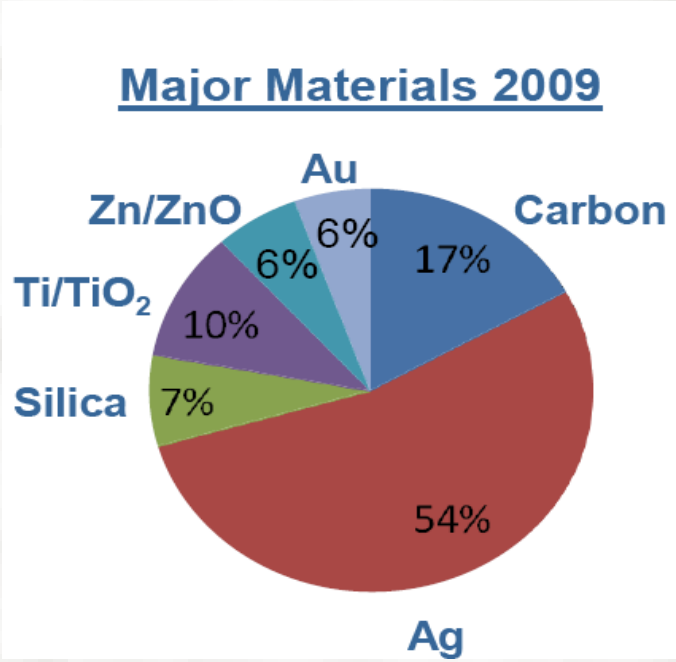




Source: ISI Web of Knowledge database, January 2008

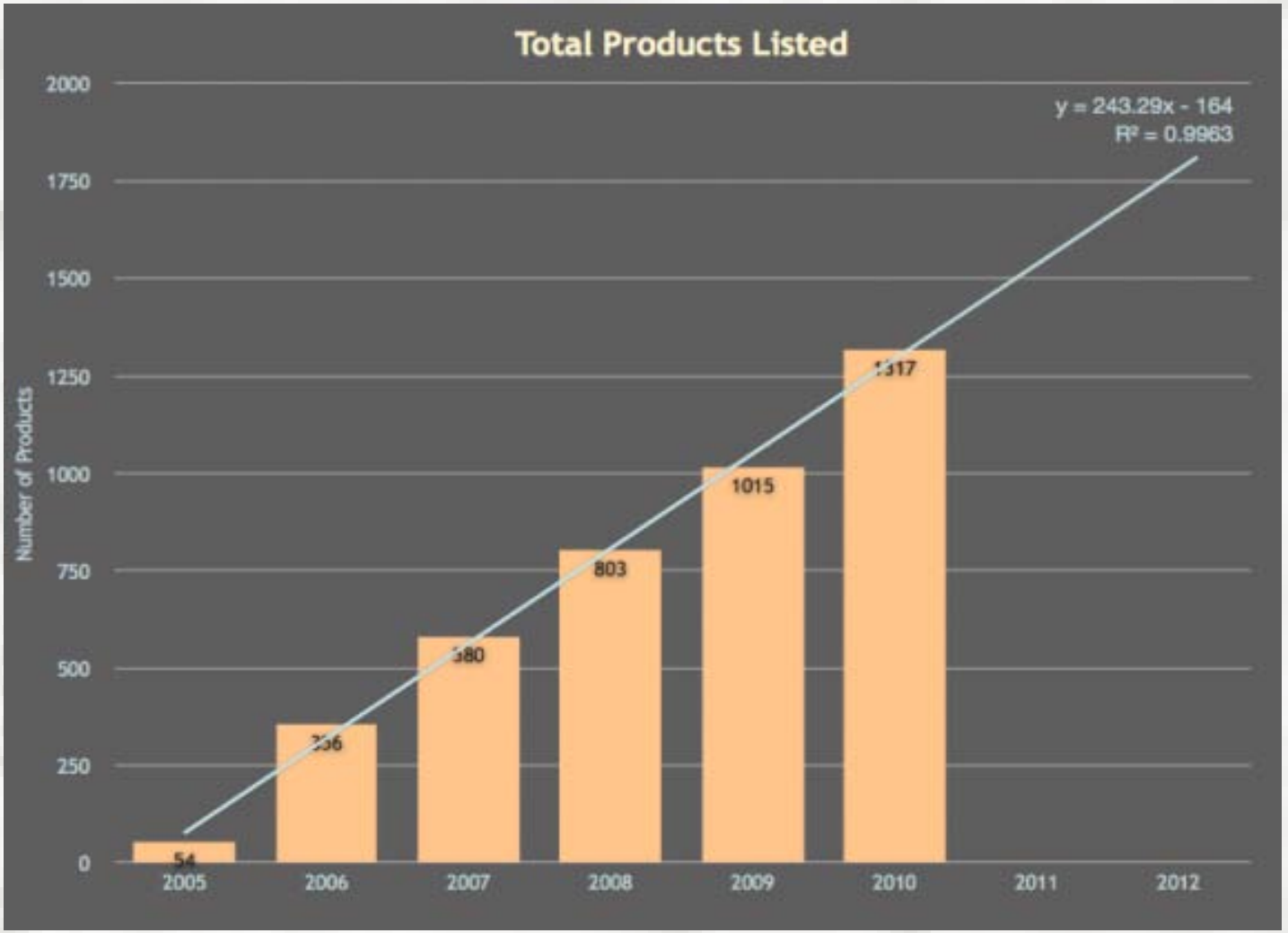
Share of patents by nanotechnology sub-areas, 1995-2005





Source: OECD Patent database, January 2008

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

WIRED SCIENCE

NEWS FOR YOUR NEURONS

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.

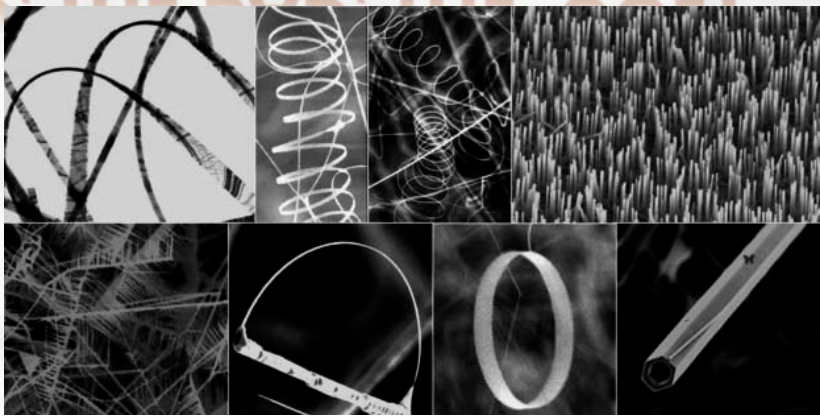
- Knowledge generation will be **incremental** and will **take time** but is worthwhile because it will lead to evidence-based decision making, safe design, and sustainability.

- 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 c1eanup cost.

NANOMATERIALS: THE GOOD, THE BAD, THE UGLY



Good:

- Nanorevolution
- Over 1000 products incorporate nanomaterials
- Projections: $3.1 trillion in global manufactured goods by 2015; 58000 tons of nanomaterials by 2020

Bad:

- Nanorevolution
- Over 1000 products incorporate nanomaterials
- Projections: $3.1 trillion in global manufactured goods by 2015; 58000 tons of nanomaterials by 2020

Ugly:

- Unpredictable and possibly severe health and environmental effects of some nanomaterials

Gulf Oil Spill

Chemicals Meant To Break Up BP Oil Spill Present New Environmental Concerns

by Abrahm Lustgarten
ProPublica, April 30, 2010, 6:44 p.m.

2 Comments | Republish | E-mail | Print

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Like 2K
Buzz up! (9)

Gulf Spill Coverage on Facebook

Photo by Chris Graythen/Getty Images

The chemicals BP is now relying on to break up the steady flow of leaking oil from deep below the Gulf of Mexico could create a new set of environmental problems.

Even if the materials,

This article is part of an ongoing investigation:

Gulf Oil Spill
The BP oil disaster in the Gulf has had untold health, economic and environmental effects.

BP Claims Tracker

Total Damage Claims from Gulf Oil Spill Paid By BP

$1,767,988,315

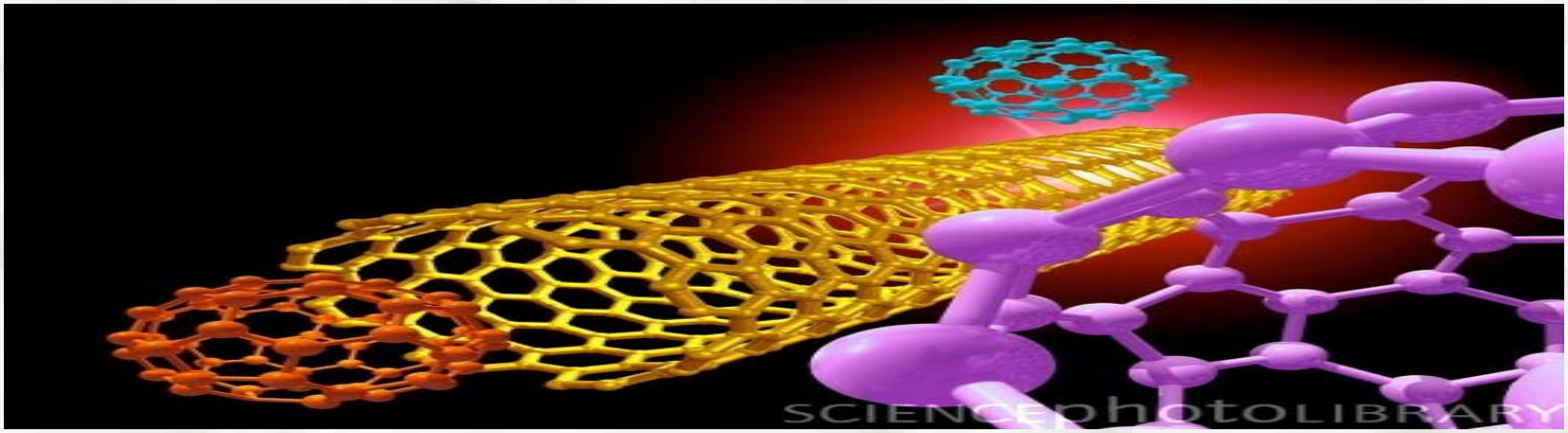
Have you filed a BP claim? Speak with a ProPublica reporter.

More Information | Get Widget

Studies if oil dispersal have found that the chemicals used can accumulate in shellfish and other organisms. (Getty Images file photo)

Paul Karason and his girlfriend, Jackie Northrup.

Challenges of Nanomaterials: Are we on the way to comprehend their toxicity?



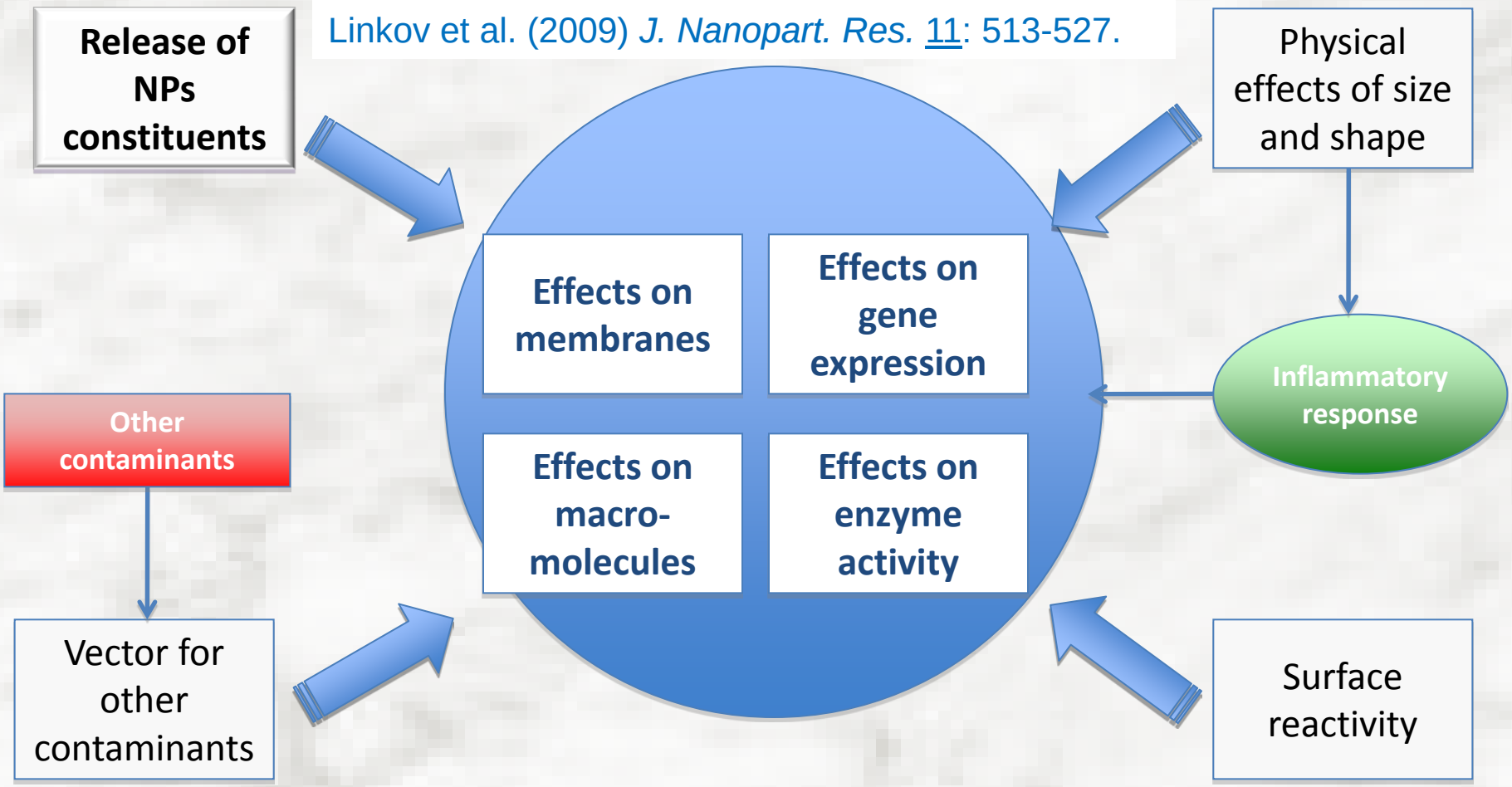
Challenges

- 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



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.

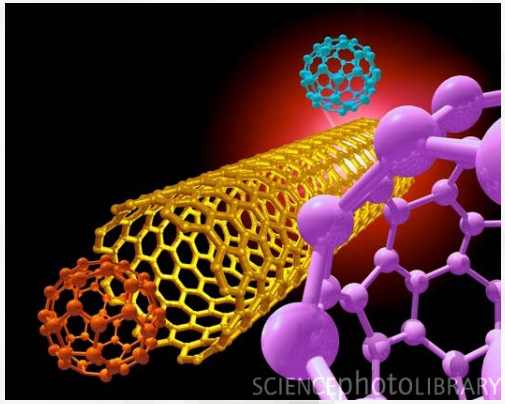
•Thus, in total about $160-320 billion and 240 thousand years total time will be needed to test chemicals currently in use.

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

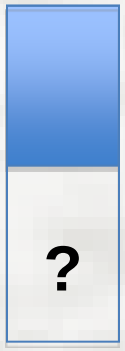
Toxicity

Biokinetic Parameters

Environmental Distribution

Basic concept of QSAR modeling

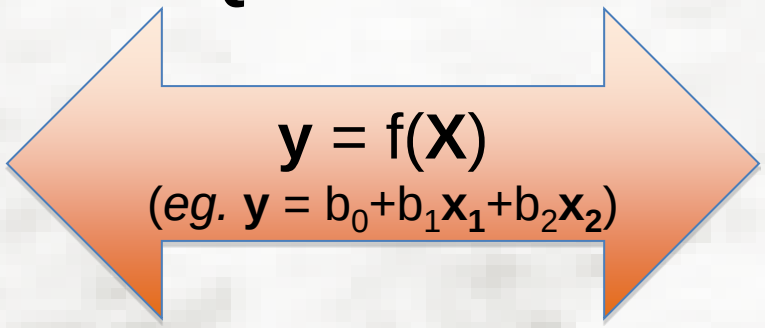
Endpoint
(experimentally measured)



y

- *Activity (EC_{50})*
- *Phys/Chem property (K_{OW}, $t_{1/2}$)*
- *Retention parameters (t_R)*
- *Toxicity (LD_{50}, LC_{50})*
- *…*

QSAR model



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

Structural descriptors

X

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

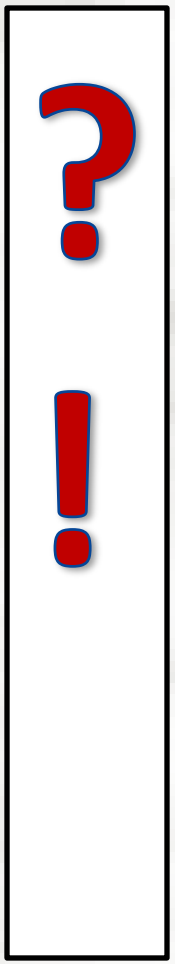
The most challenging problems for Nano-QSAR

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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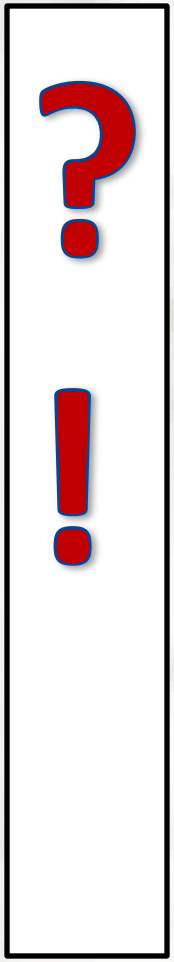
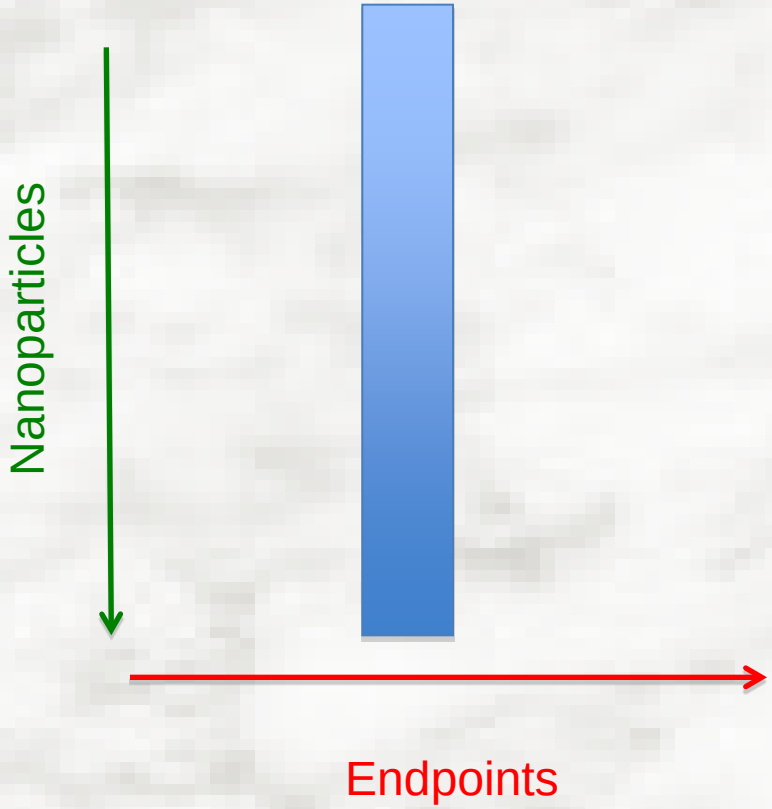
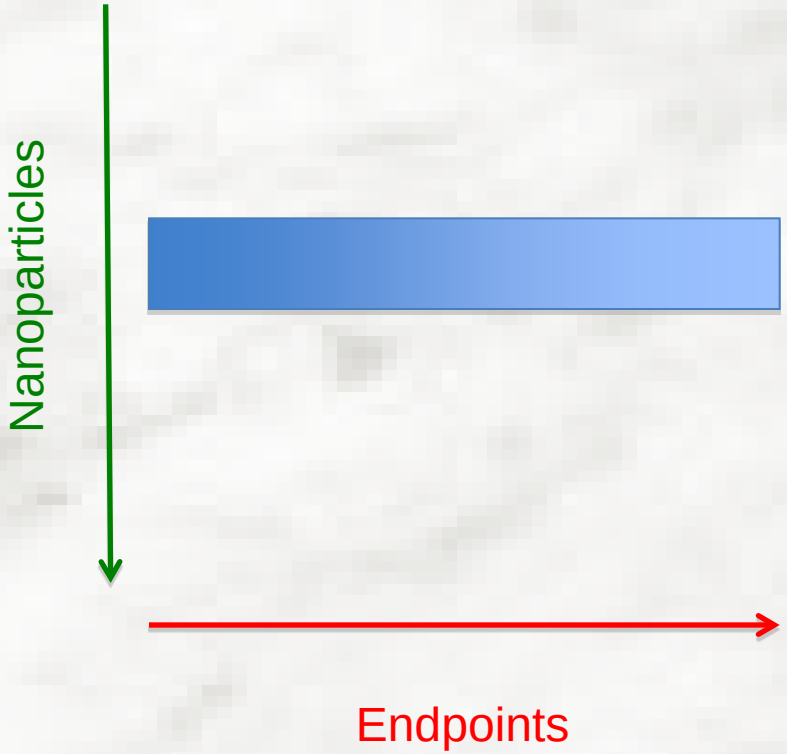


Experimentalists vs. QSAR modelers



Data for QSAR

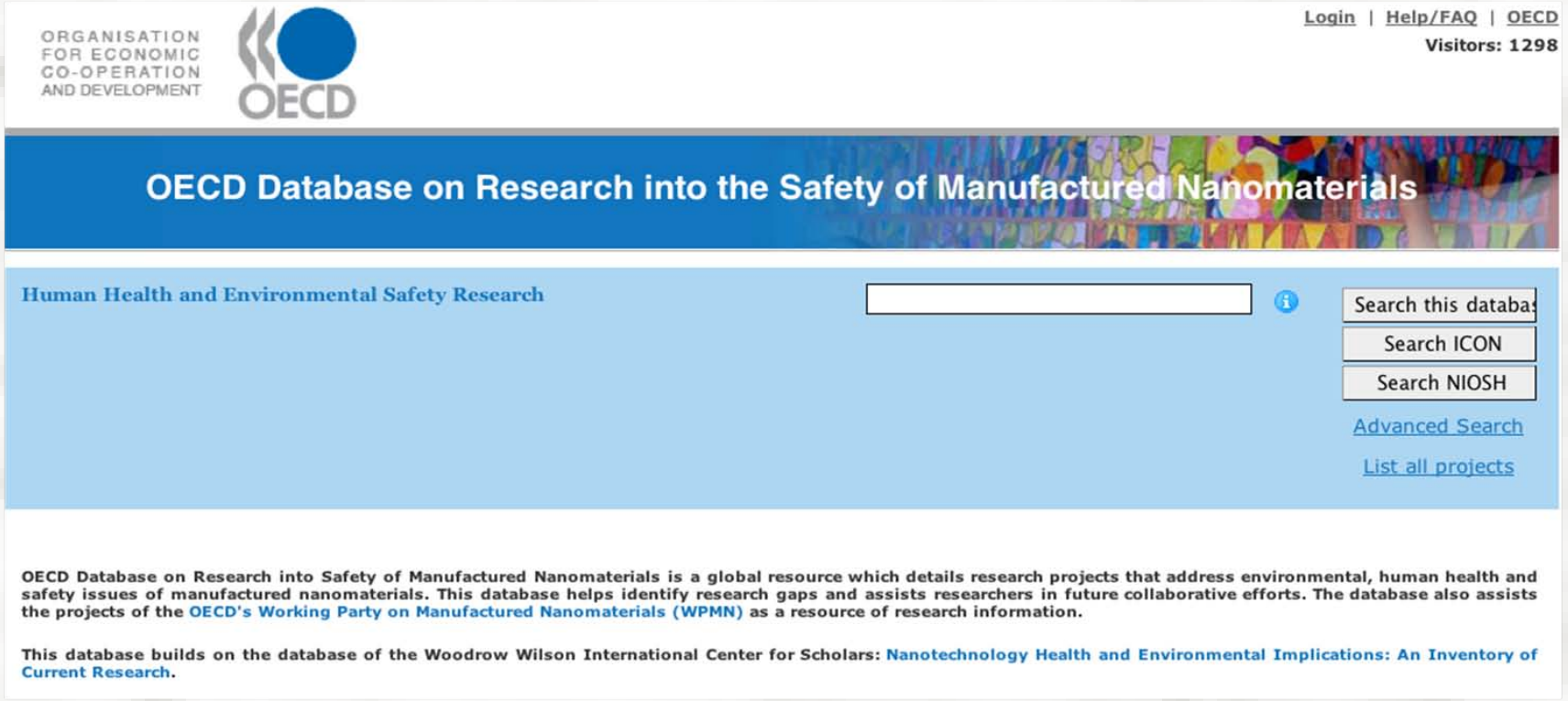


Data from experiments

Existing databases

OECD database

http://webnet.oecd.org/NanoMaterials/Pagelet/Front/Default.aspx?



JRC NANOhub database

(http://www.napira.eu)

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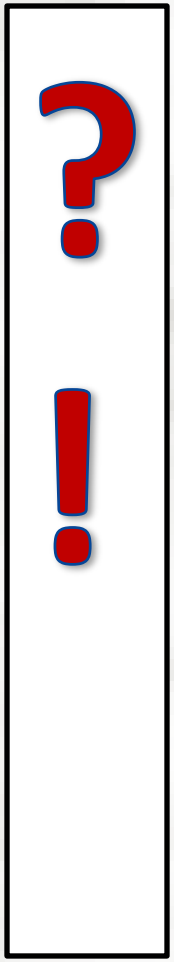
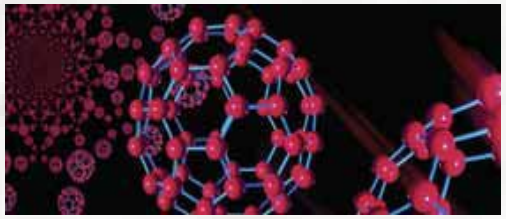
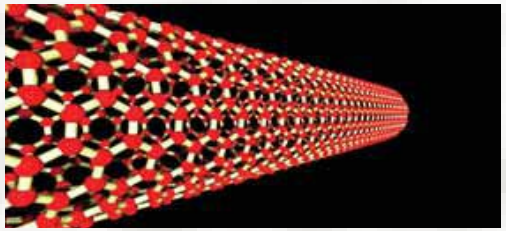
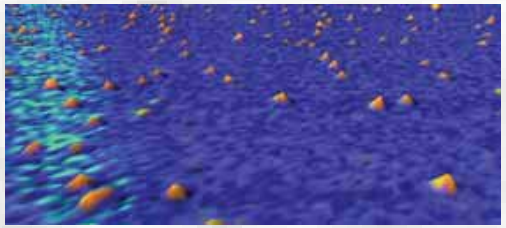


Specific structural features of NPs

Oberdörster et al. *Particle and Fibre Toxicol. 2: 8.*





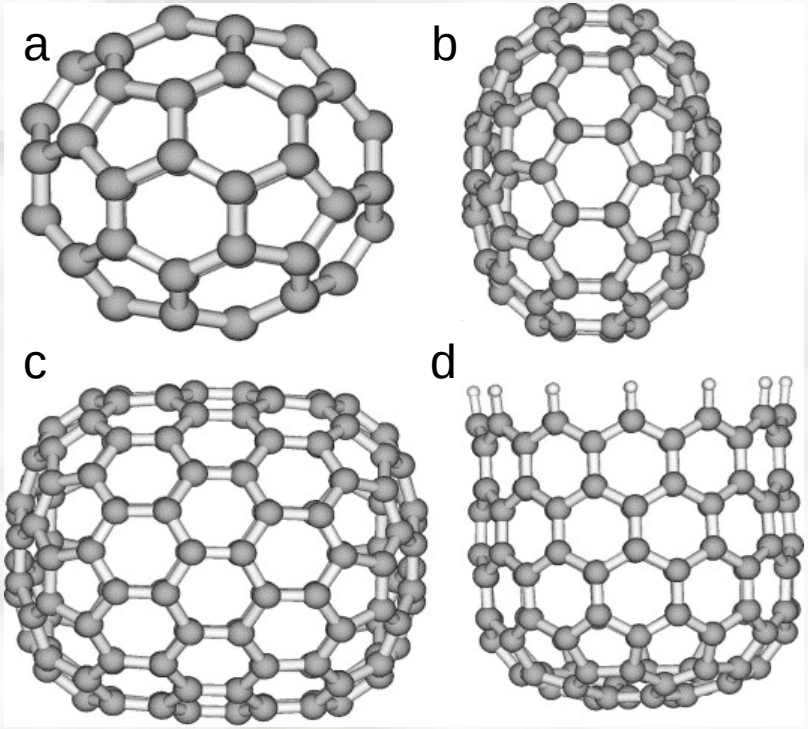


Toxicity of NPs can be related to:

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

Calculating 3D descriptors based on the whole system

Shukla, Leszczynski (2006) *Chem. Phys. Lett.* 428: 317-320.



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

#	Structure	HOMO-LUMO gap [eV]	IP [eV]	EA [eV]
a	Fullerene C_{60}	2.77	7.24	1.75
b	Disk C_{96}	1.53	6.46	2.98
c	Capsule C_{144}	1.25	6.72	3.46
d	Bowl $C_{120}H_{12}$	0.46	5.19	3.75

Experimental techniques that can be used to obtain nano-descriptors

Haselov et al. (2008) *Ecotoxicology* 17: 344-361.

Properties	Instruments and methods*
Diameter	EM, AFM, Flow-FFF, DLS
Volume	Sed-FFF
Area	EM, AFM
Surface charge	z-Potential, electrophoretic mobility
Crystal structure	XRD, TEM-XRD
Elemental composition	Bulk: ICP-MS, ICP-OES Singe nanoparticle: TEM-EDX Particle population: FFF-ICP-MS
Aggregation state	DLS, AFM, ESEM
Hydrophobicity	Liquid-liquid extraction chromatography
Hydrodynamic diameter	Flow-FFF, DLS
Equivalent poresize diameter	Particle filtration

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.

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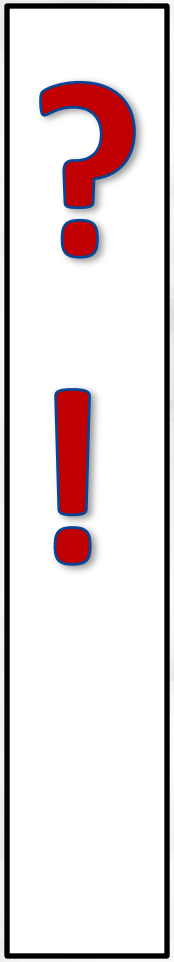
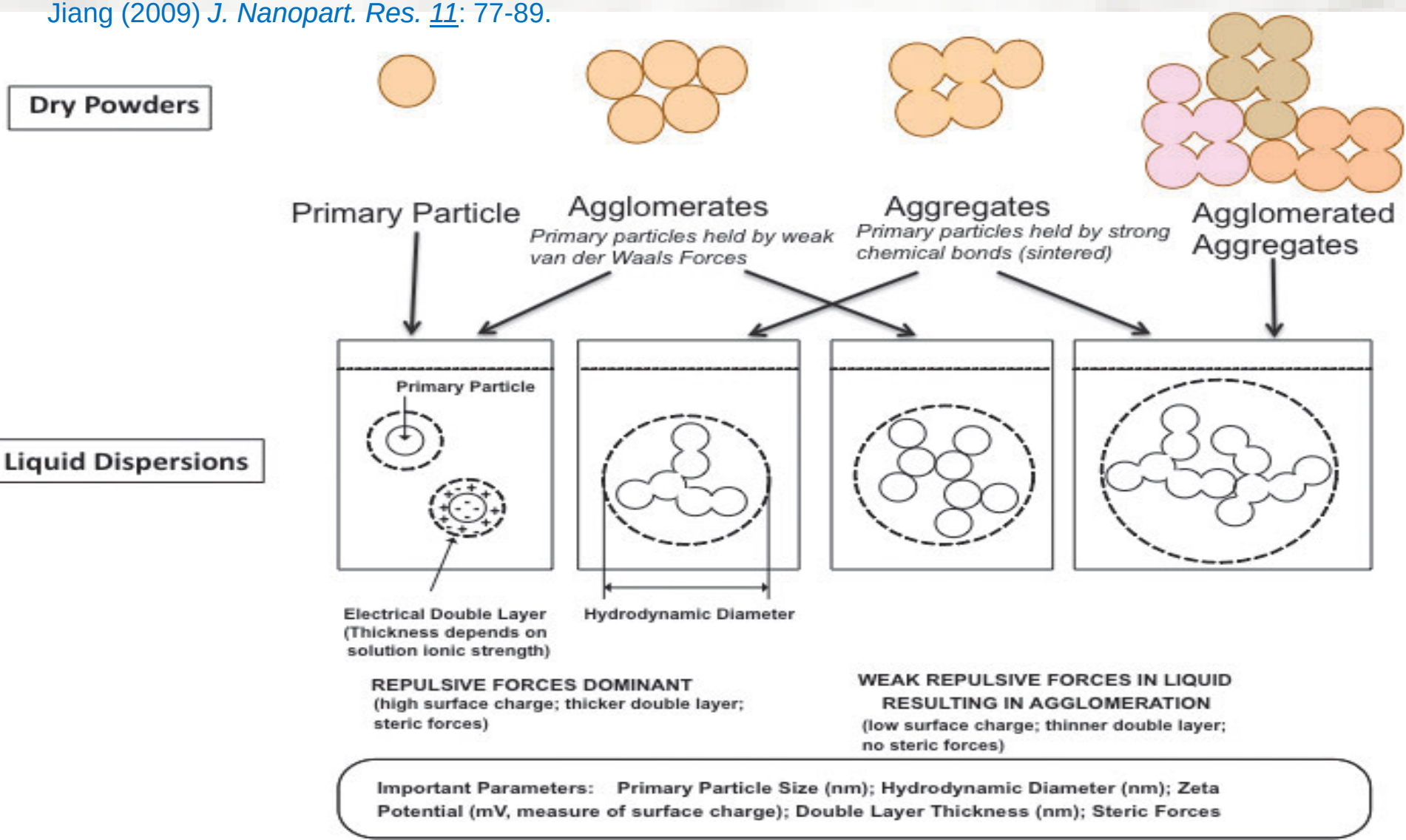


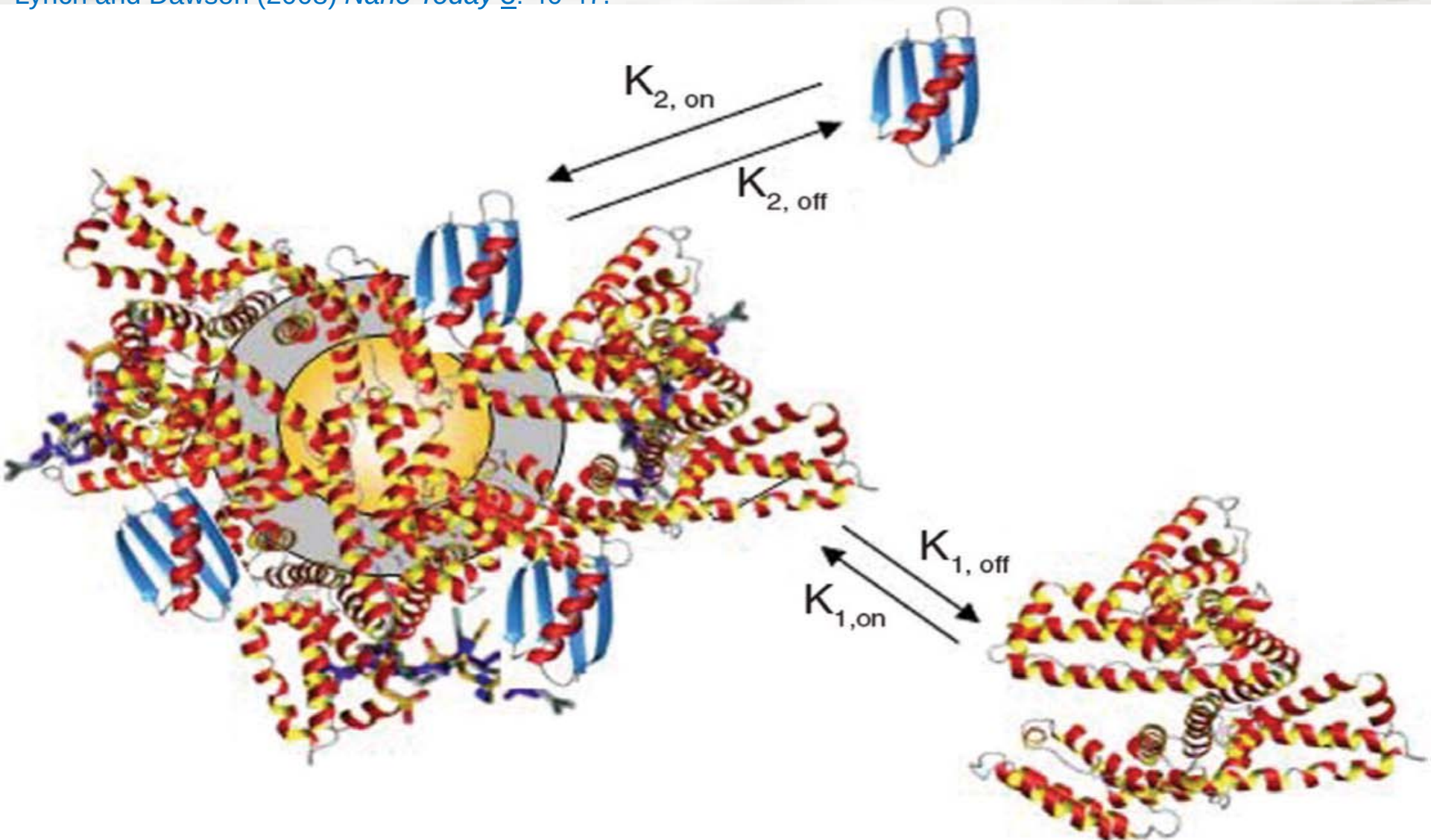
Agglomeration and aggregation of NPs

Jiang (2009) *J. Nanopart. Res.* 11: 77-89.



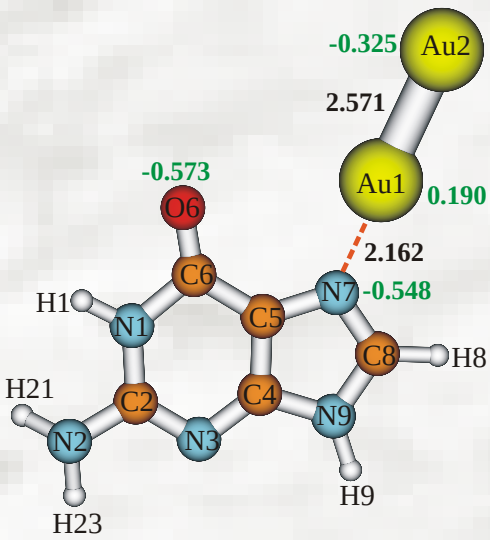
Formation of protein coronas

Lynch and Dawson (2008) *Nano Today* 3: 40-47.

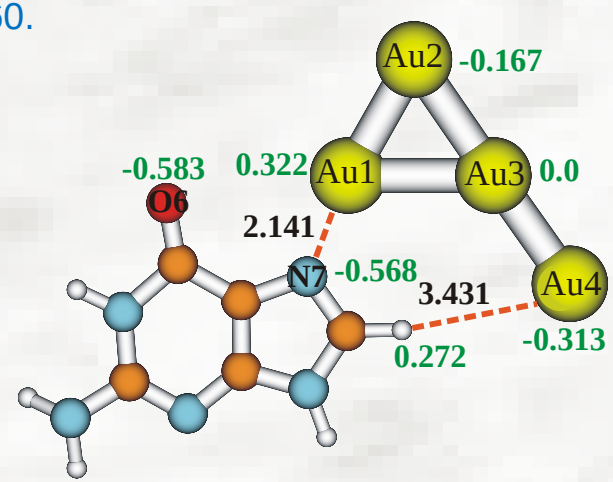


Optimized Structures of G-Au$_n$ and GC-Au$_n$

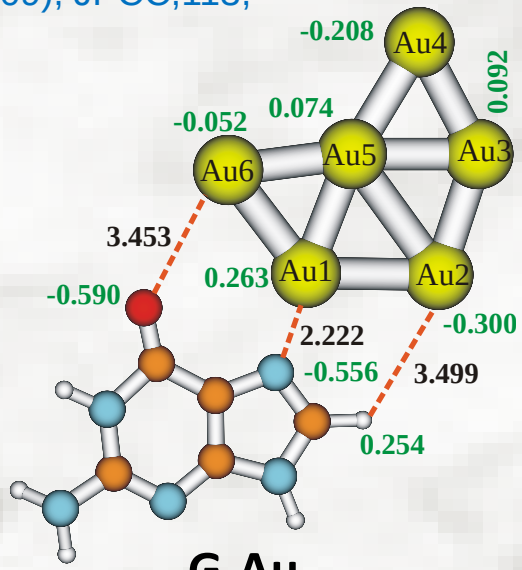
M.Shukla, M.Dubey, E. Zakar J.Leszczynski, (2009), JPCC,113, 3960.



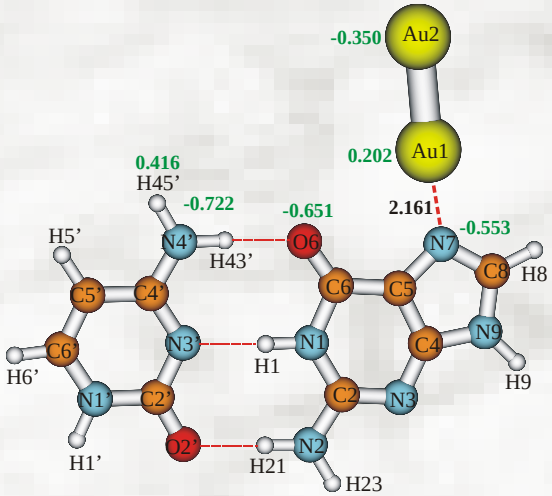
G-Au$_2$



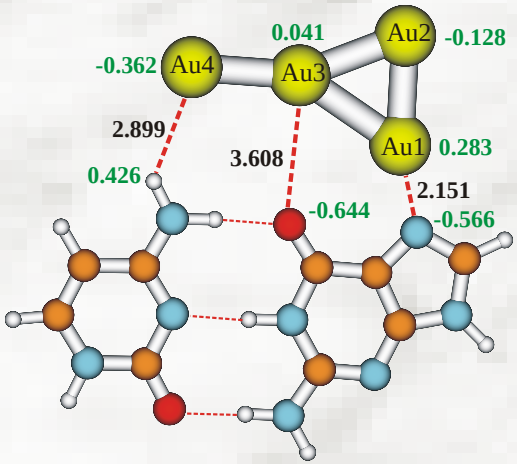
G-Au$_4$



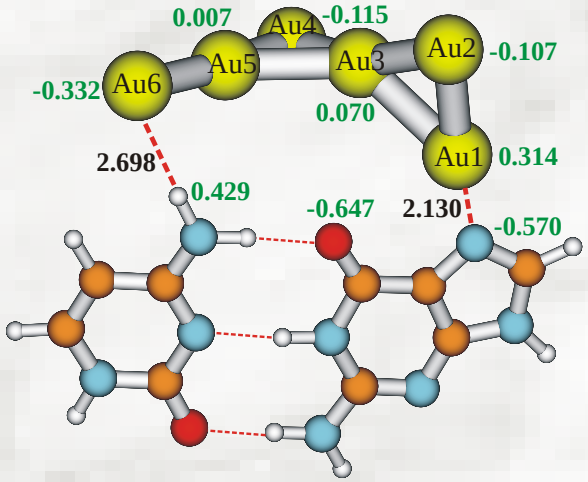
G-Au$_6$



GC-Au$_2$



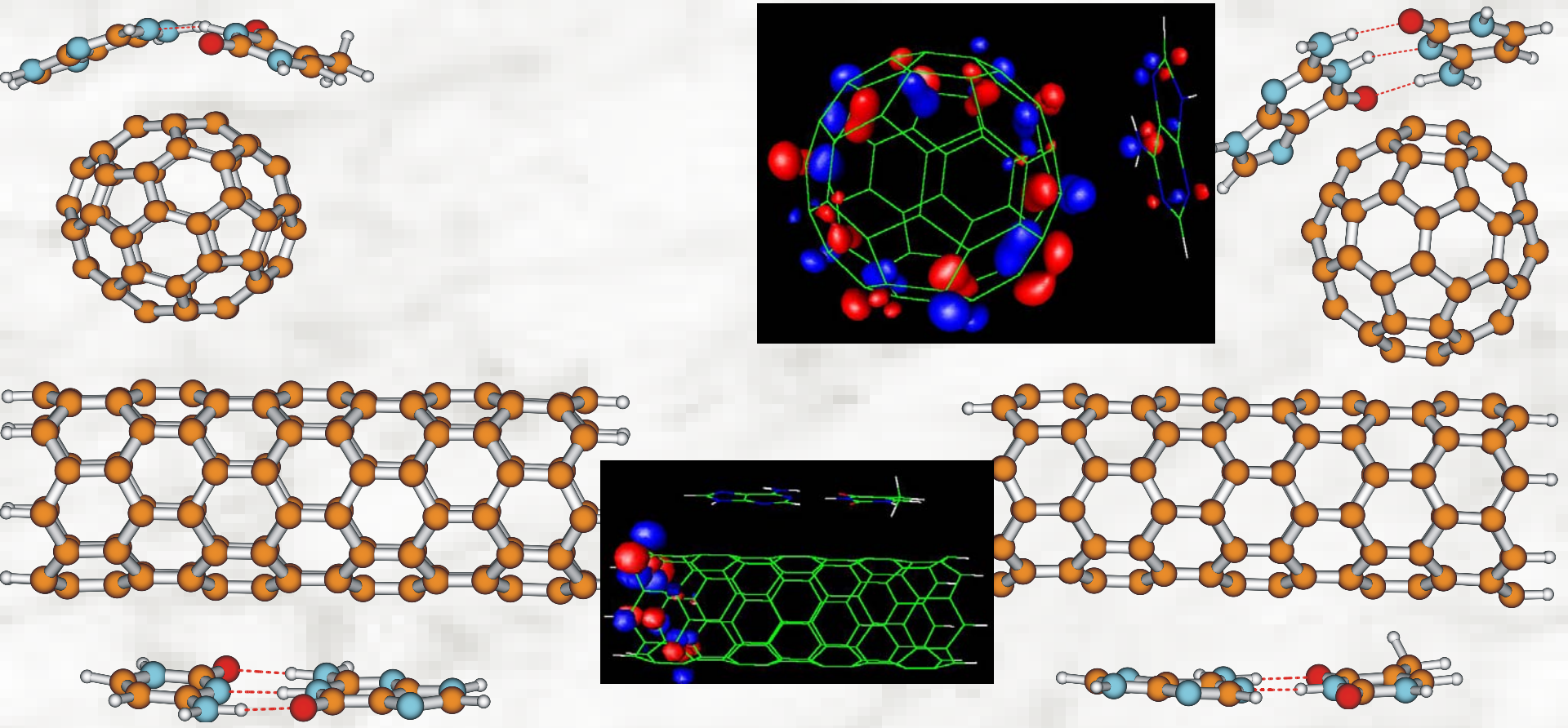
GC-Au$_4$



GC-Au$_6$

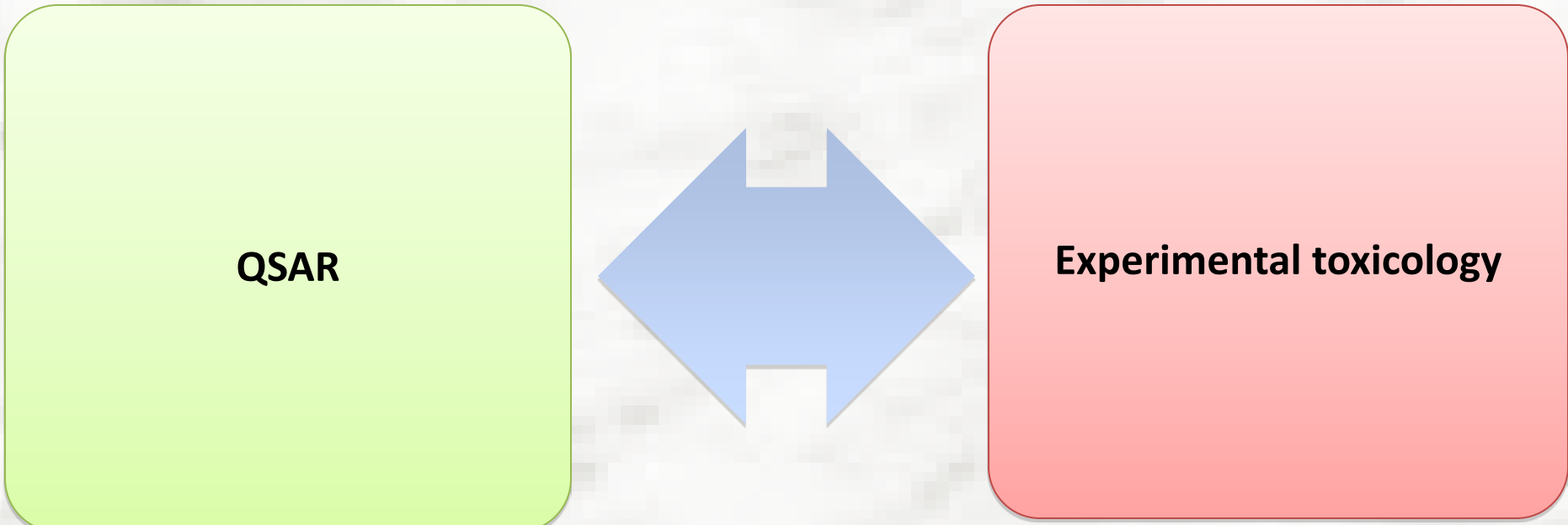
NBO charges for selected atoms are given in green color while selected gold atoms and base distances are in Å.

Interactions of G, GC and AT with C_{60} and SWNT

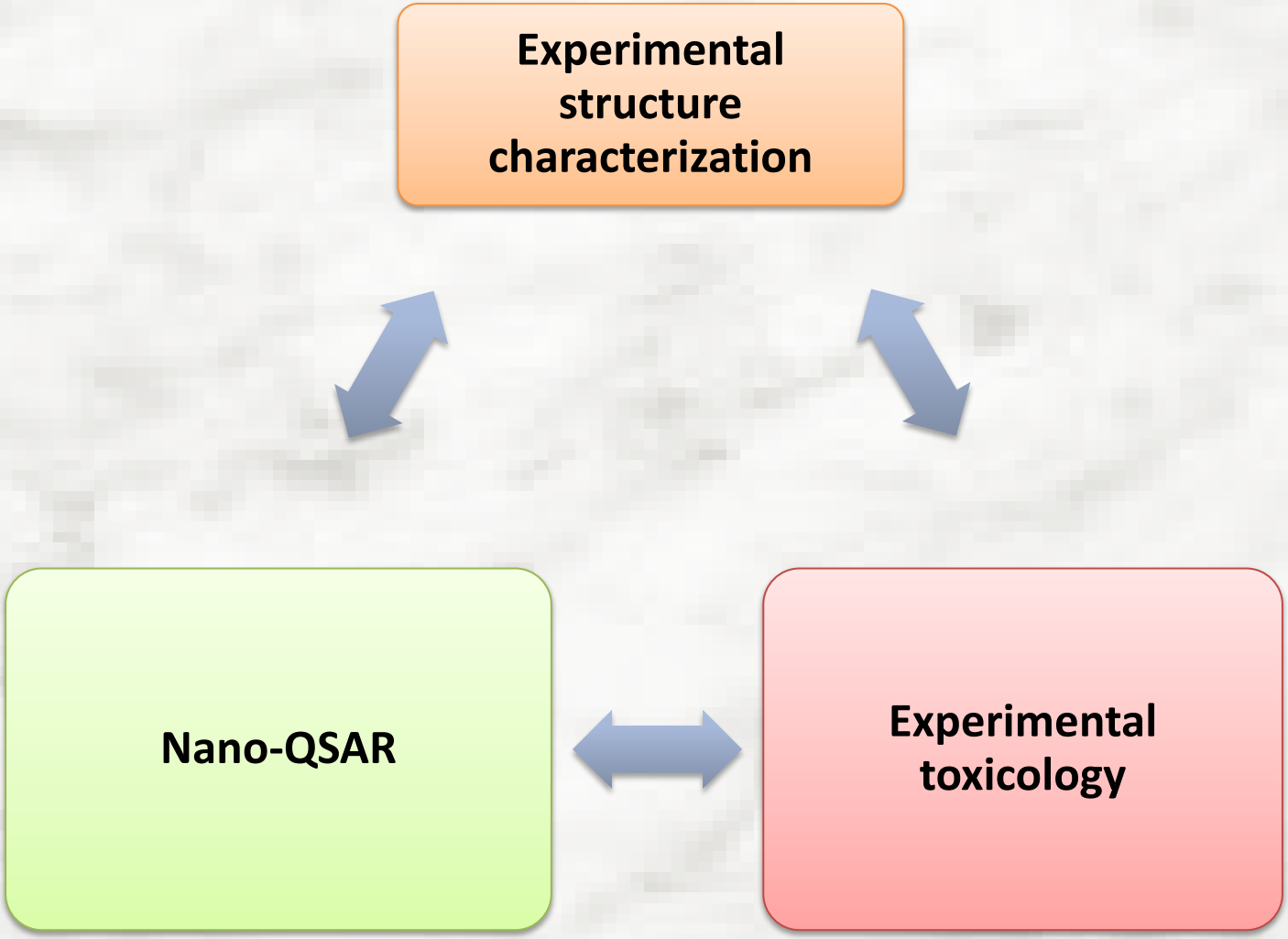


M.Shukla, J.Leszczynski, (2009), CPL, 469, 27; ibid (2010), 493,126; ibid (2010), 496, 130

Collaboration within „classic" QSAR studies



What we need to develop Nano-QSARs?



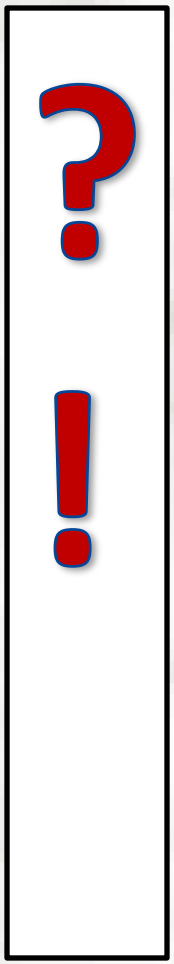
The most challenging problems for Nano-QSAR

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

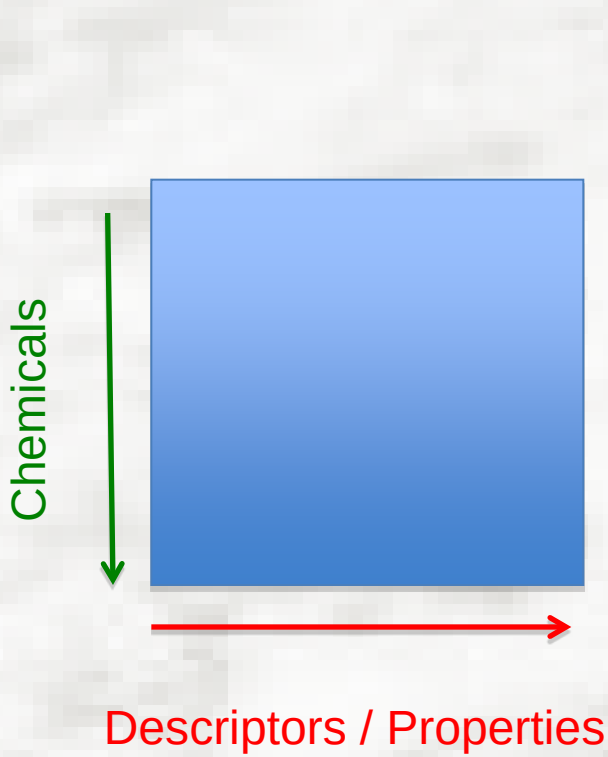
2. Lack of appropriate descriptors able to express specificity of nano-structure

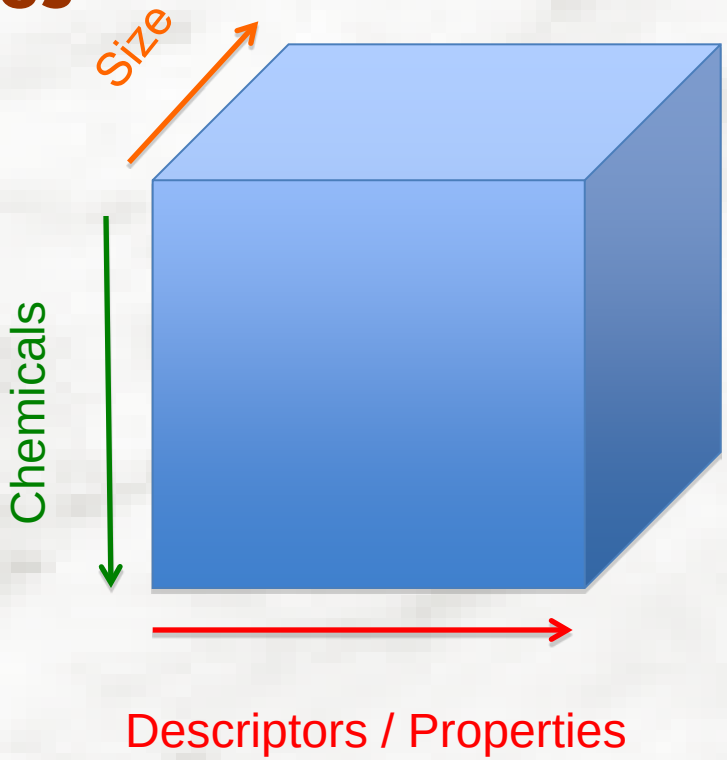
3. Limited knowledge on the interactions between NPs and dispersants as well as biological systems (DNA, proteins, membranes etc.)

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



Data for „classic" QSAR and Nano-QSAR studies



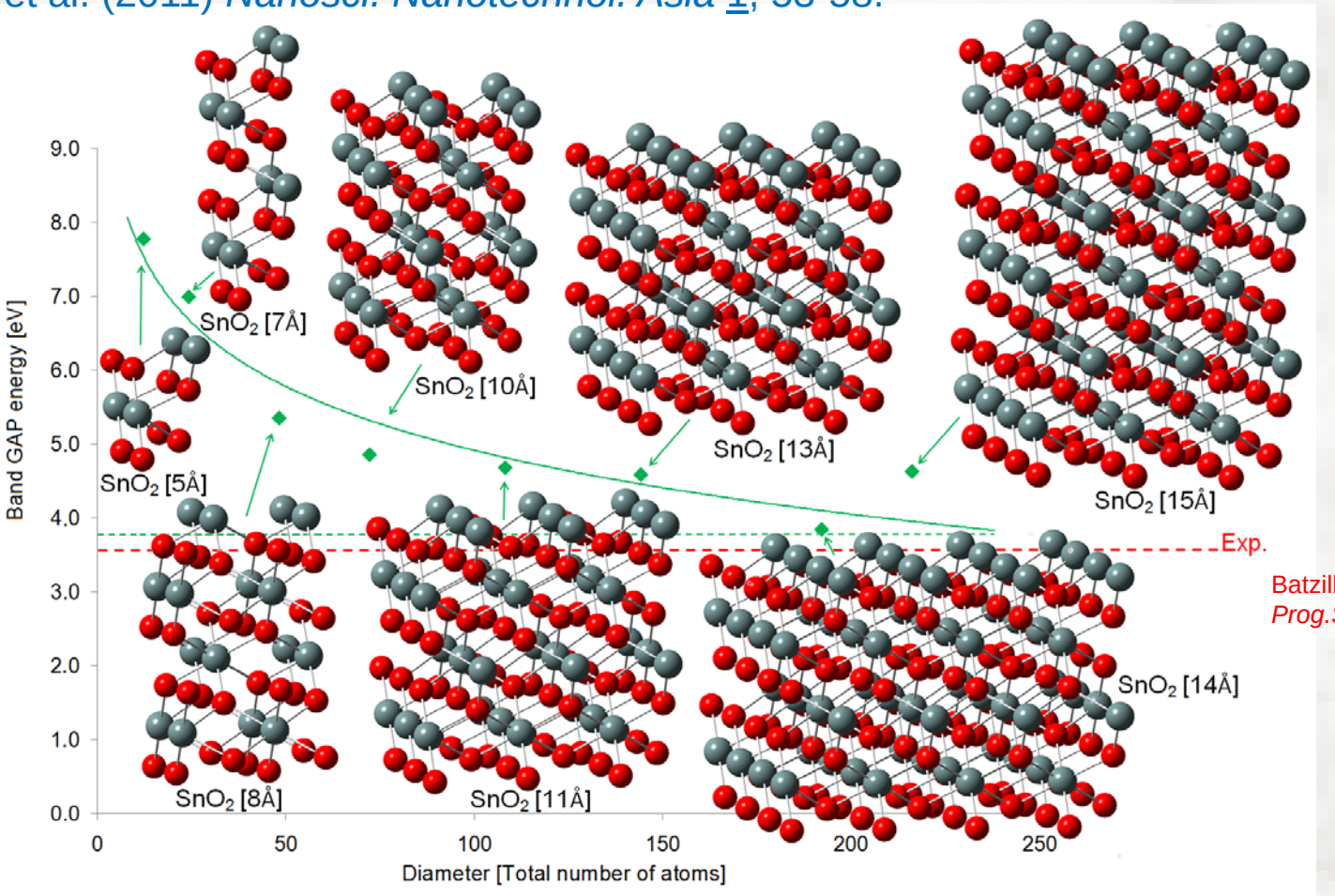


„Classic" QSAR

Nano-QSAR

Size-dependence of QM properties/descriptors [1]

Gajewicz et al. (2011) *Nanosci. Nanotechnol. Asia* 1, 53-58.

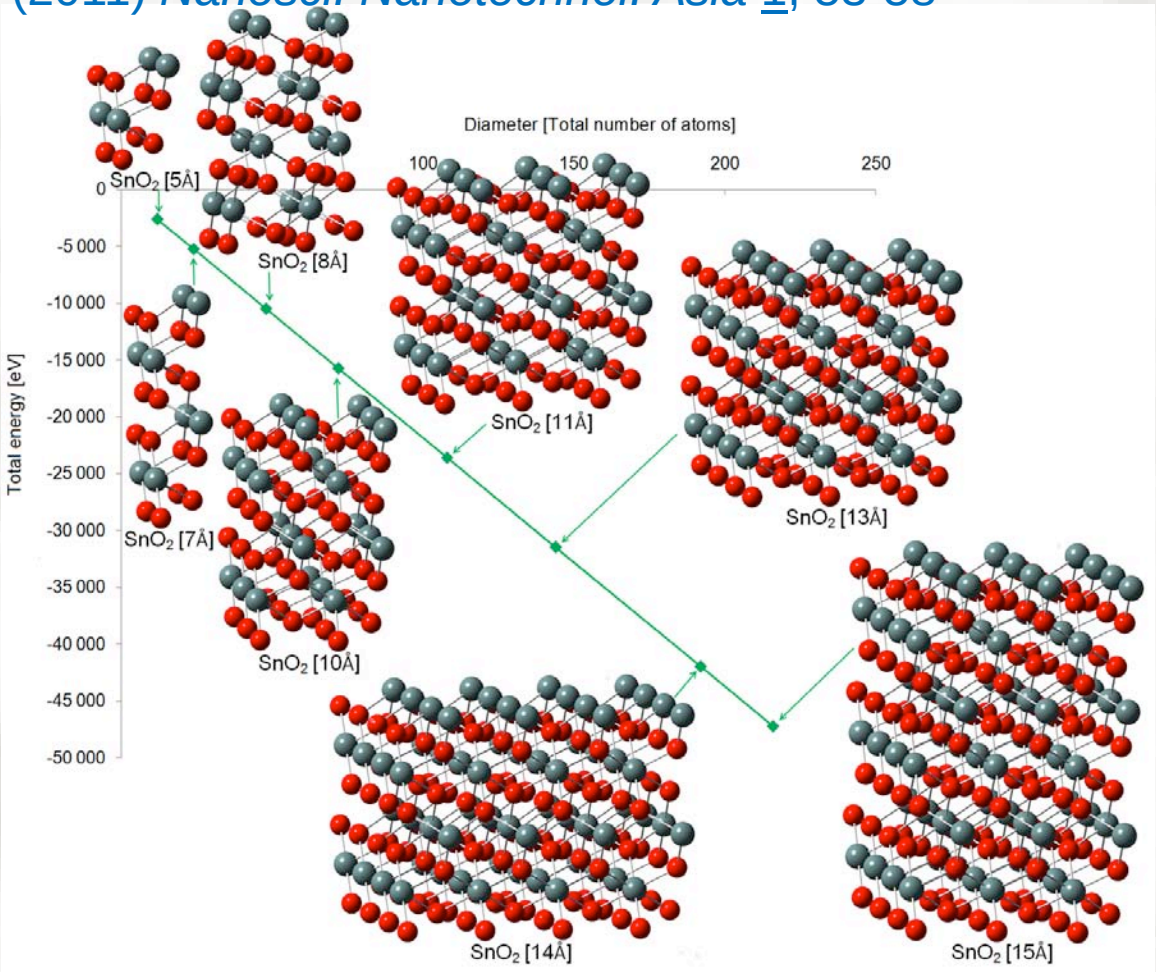


Batzill, Diebold (2005) *Prog.Surf. Sci.* 79, 47-1

Scheme A: GAP, HOMO, LUMO, hardness, softness, electrophilicity

Size-dependence of QM properties/descriptors [2]

Gajewicz et al. (2011) *Nanosci. Nanotechnol. Asia* 1, 53-58



Scheme B: HOF, total energy, electronic energy, SAS, dipole moment

Preliminary QSAR model predicting cytotoxicity of nano-sized oxides particles to *E. coli* [1]

0.1038/NNANO.2011.10

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

Tomasz Puzyn[1,2], Bakhtiyor Rasulev[1], Agnieszka Gajewicz[1,2], Xiaoke Hu[3], Thabitha P. Dasari[3], Andrea Michalkova[1], Huey-Min Hwang[3], Andrey Toropov[4], Danuta Leszczynska[5] and Jerzy Leszczynski[1]*

It is expected that the number and variety of engineered nanoparticles will increase rapidly over the next few years[1], and there is a need for new methods to quickly test the potential toxicity of these materials[2]. 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 data[6], 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 health[6]. 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 environment[7].

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]

Puzyn et al. (2011) *Nature Nanotechnol.* 6, 175-178.

- 17 oxides NPs: ZnO, CuO, V_2O_3, Y_2O_3, Bi_2O_3, In_2O_3, Sb_2O_3, Al_2O_3, Fe_2O_3, SiO_2, ZrO_2, SnO_2, TiO_2, CoO, NiO,Cr_2O_3, La_2O_3

- Empirical testing protocol:
  X. Hu et al. (2009) *Sci. Total Environ.* 407: 3070-3072.

- 12 electronic descriptors calculated at the semi-empirical PM6 level

Preliminary QSAR model predicting cytotoxicity of nano-sized oxides particles to *E. coli* [3]

Puzyn et al. (2011) *Nature Nanotechnol.* 6, 175-178.

$$\log\left(1/LC_{50}\right) = 2.59(\pm 0.07) - 0.50(\pm 0.07)\cdot \Delta H_{Me+}$$

n = 10, n_{test} = 7,

F = 45.4, p < 0.001,

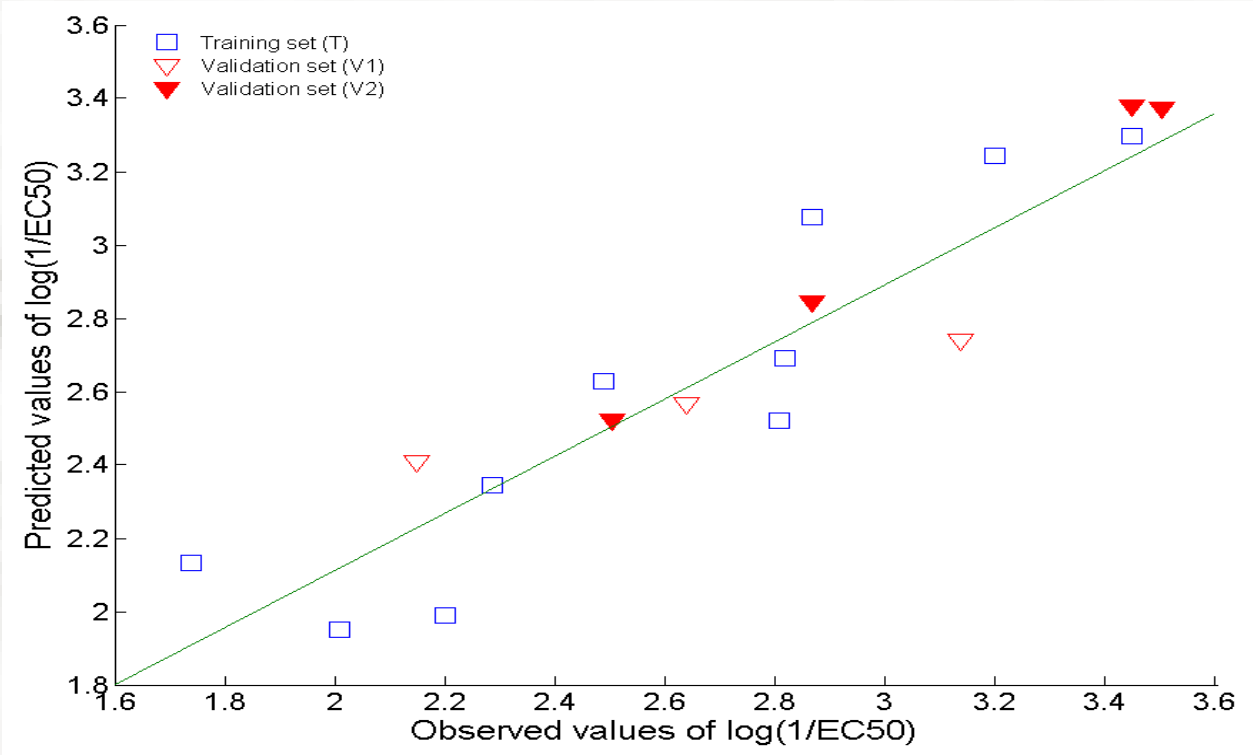
R^2 = 0.85, Q^2_{CVLOO} = 0.77,

Q^2_{test} = 0.83,

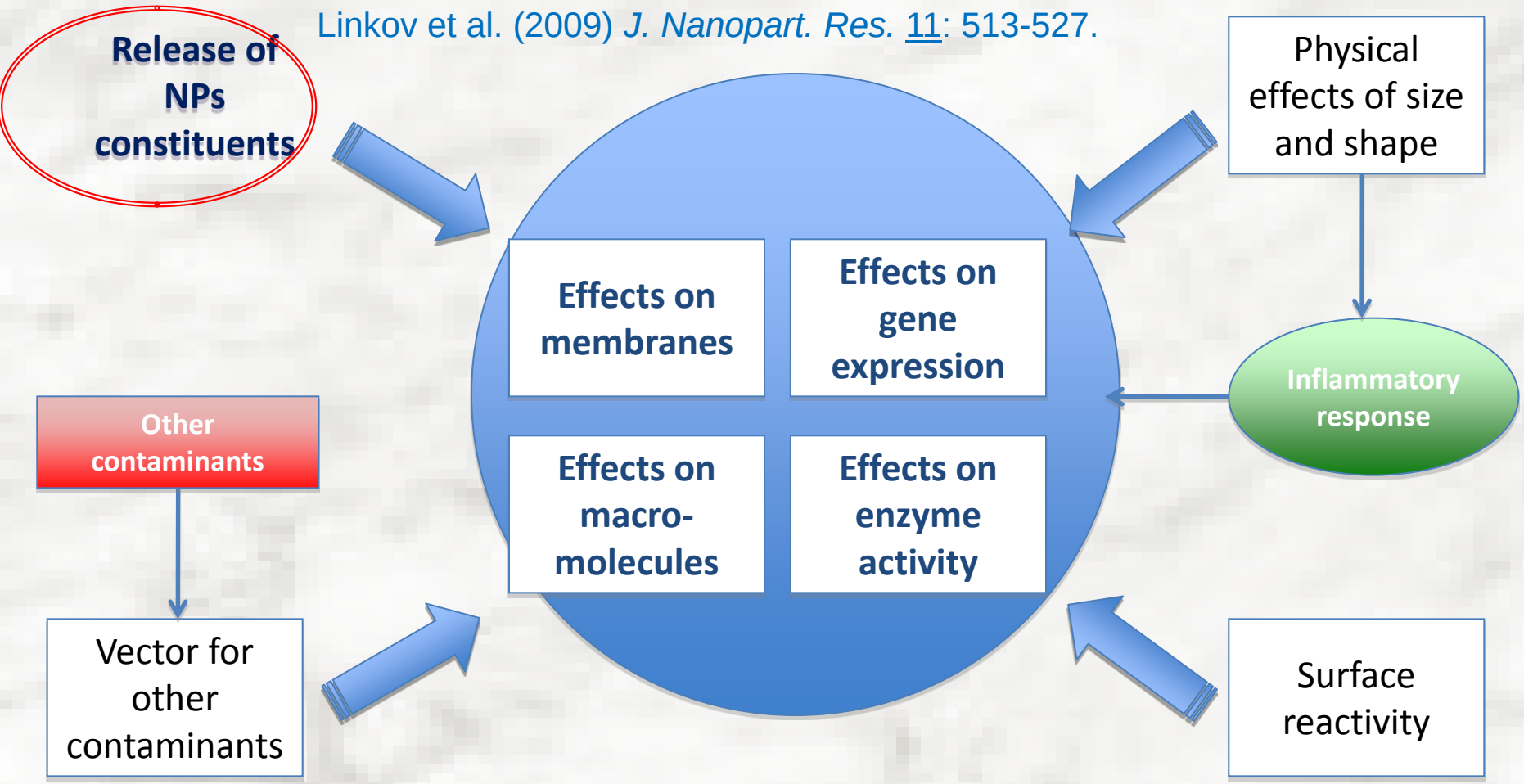
RMSEC = 0.20,

RMSECV = 0.24,

RMSEP = 0.19



Postulated mechanisms of NPs' toxicity



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 toxicology 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"[1], and the sheer diversity of nanotoxicology can be seen on a web page that contains links to all the articles that *Nature Nanotechnology* has published on the subject[2]. 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[3].

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 toxicology 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[4]. 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[3] and they may exemplify 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 release 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[5].

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 the cell 'sees' the nanoparticle[6]. It has also been shown that certain nanoparticles can induce proteins to unfold, leading to an inflammatory response[7]. Similarly, nanoparticles are coated with natural organic matter when they enter water, soil or sediment environments and this layer influences their reactivity, bioavailability and other transformations in the environment[8]. 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[9]. 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[10]; there are also opportunities for computational scientists to develop appropriate structural parameters for describing nanomaterials and to work with toxicologists to design new assays[11].

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[12]. 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

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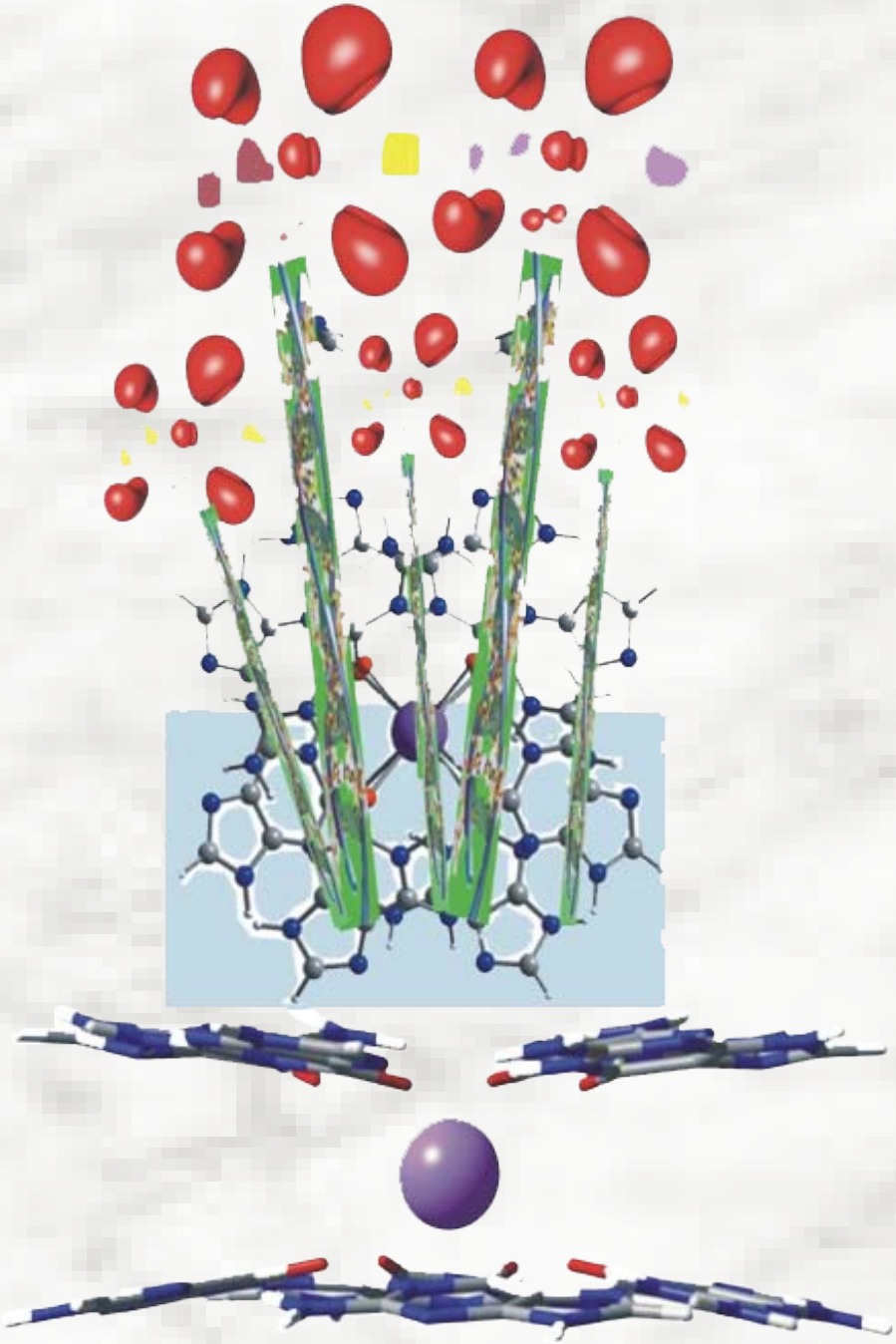
11. Burello, E. & Worth, A. *Nature Nanotech.* **6**, 138–139 (2011).
12. http://characterizationmatters.org/parameters/



Thank you

for your attention!