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QSARs for nanomaterials: current status and perspectives

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Outline

- QSAR and other computational methods for predicting the toxicity of NMs
- Challenges
- CMS 2012 project @ TNO (Computational Material Science)
- Discussion/Outlook


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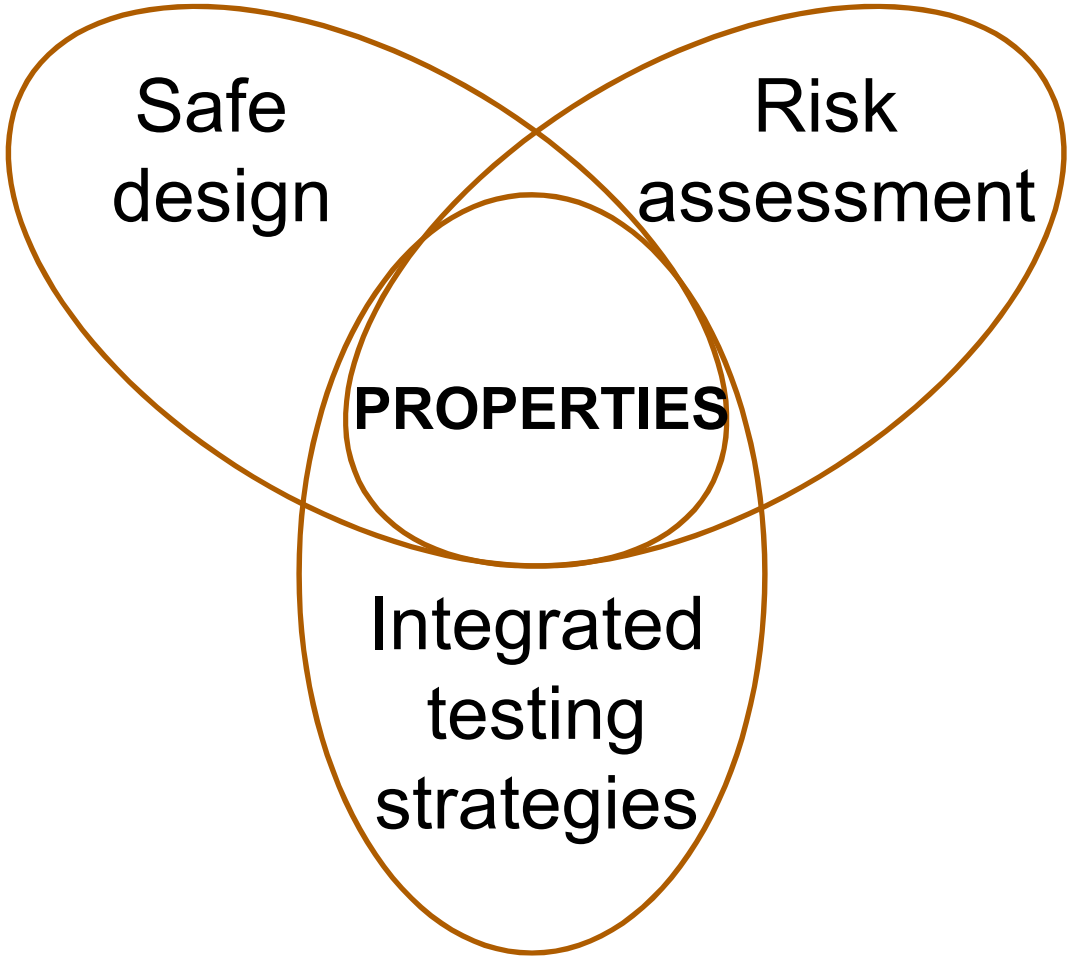
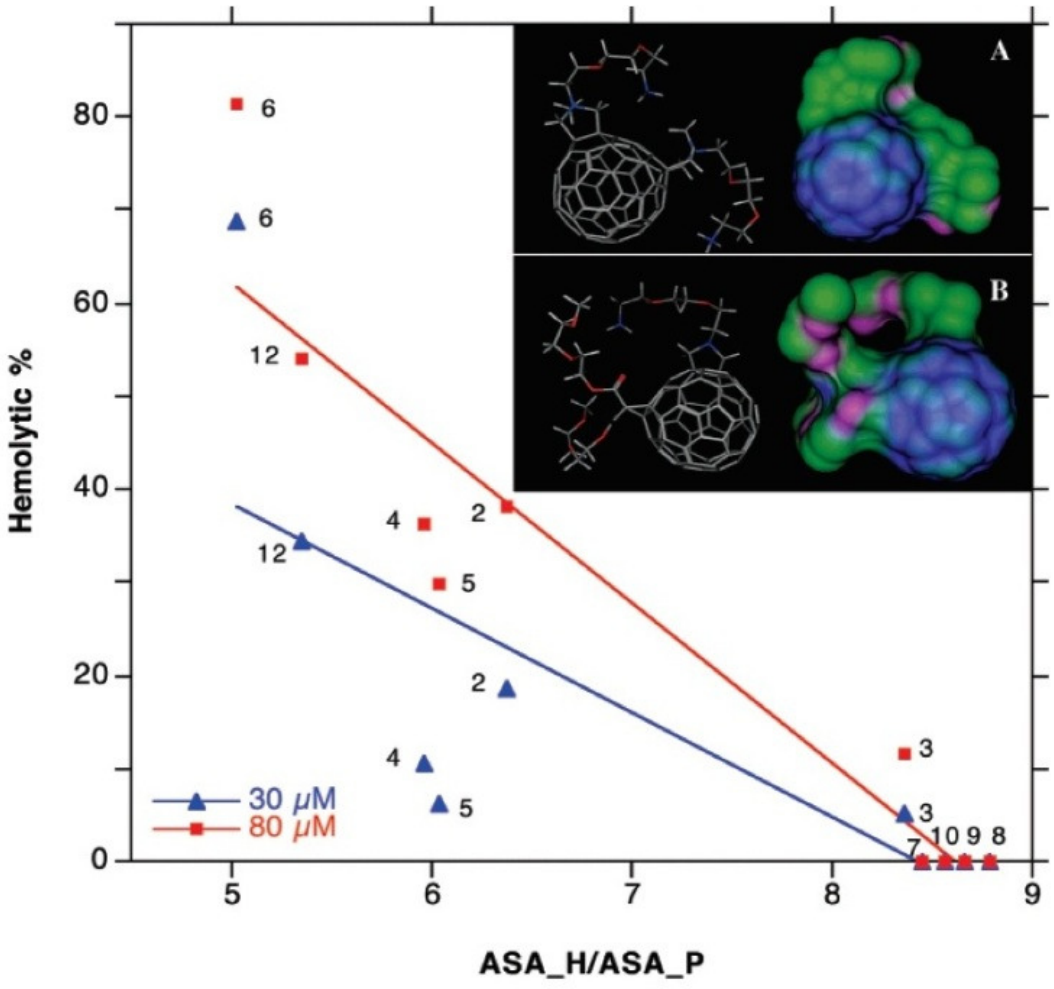
Hazardous properties of NMs

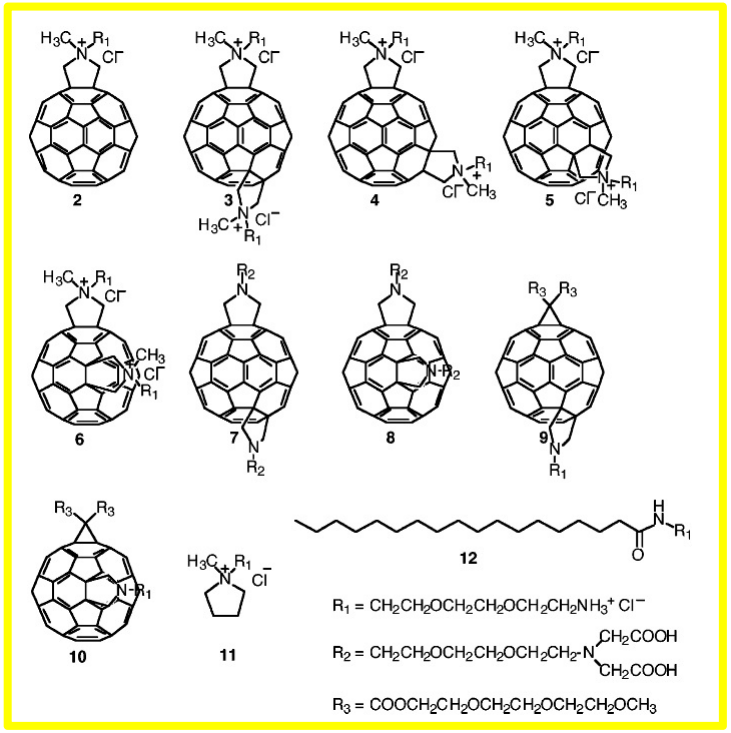



Computational methods and models relevant for RA, SD, ITS

- SARs/QSARs/QSPR
- Mathematical modeling
- Mechanistically-based models
- Molecular modeling and simulation
- Other property/activity relationships from other research areas (surface science, biomaterials …)

QSAR models – 1





Bosi S, Feruglio L, Da Ros T, Spalluto G, Gregoretti B, Terdoslavich M, Decorti G, Passamonti S, Moro S, Prato M. Hemolytic effects of water-soluble fullerene derivatives. *J Med Chem* 2004, 47:6711–6715.

QSAR models – 2

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

CYTOTOXICITY

Me^{2+}

$$Me_{(s)} \rightarrow Me^{n+}_{(g)} + n\cdot \bar{e} \qquad \Delta H_{Me+}$$

$$\Delta H_{Me+} = \Delta H_S + \sum_{i=1}^{n} IP_i$$

Me^{3+}

$$a\cdot Me^{n+}(g) + b\cdot O^{2-}(g) \rightarrow Me_aO_b(s) \qquad \Delta H_L$$

Me^{4+}

$$\bar{e} + O_2 \longrightarrow O_2^-$$

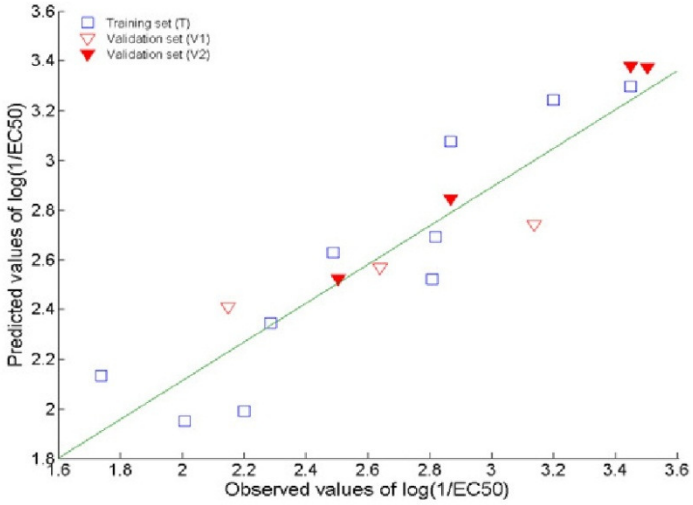
$$O_2^- + 2H^+ + \bar{e} \longrightarrow H_2O_2$$

$$H_2O_2 + O_2^- \longrightarrow OH^\bullet + OH^- + O_2$$

ROC

ZnO, CuO, V2O3, Y2O3, Bi2O3, In2O3, Sb2O3, Al2O3, Fe2O3, SiO2, ZrO2, SnO2, TiO2, CoO, NiO,Cr2O3, La2O3

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



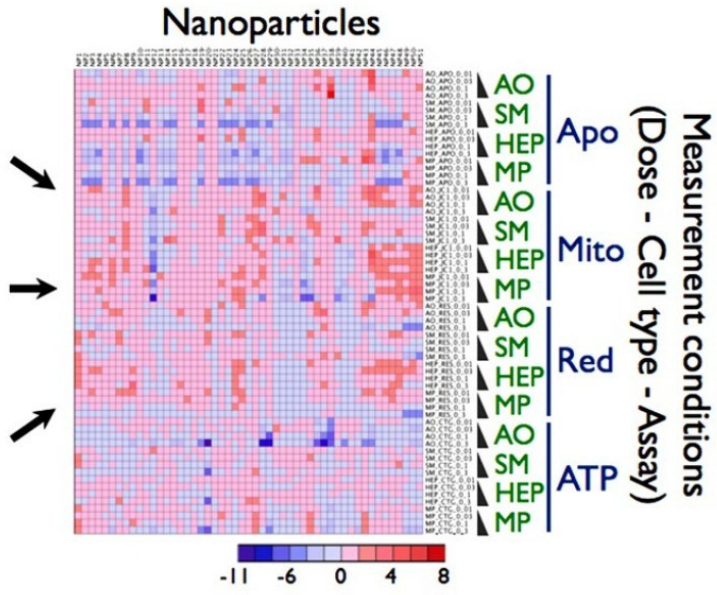
Puzyn et al. (2011) *Nature Nanotechnol.* 6, 175-178.

QSAR models – 3

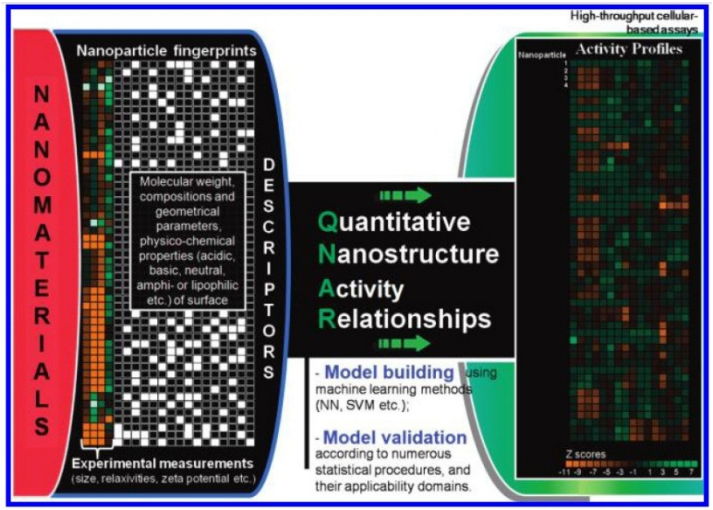
Nanoparticles (n=50)
- 4 doses
- include commercially available and in human use

Cell types
- endothelial
- vascular smooth muscle
- monocyte/macrophage
- hepatocyte

Cell-based assays
- apoptosis
- mitochondrial potential
- reducing potential
- ATP content

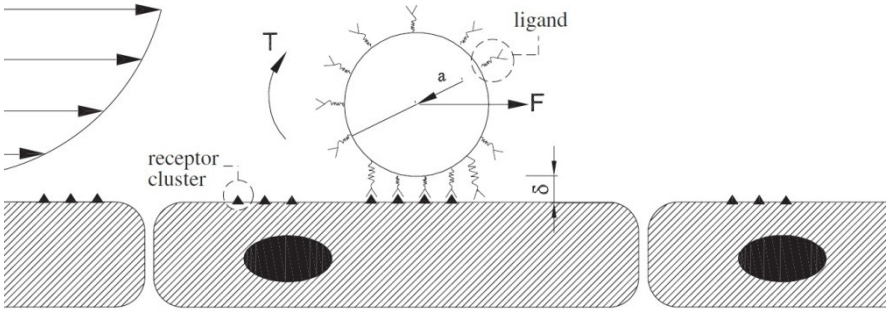


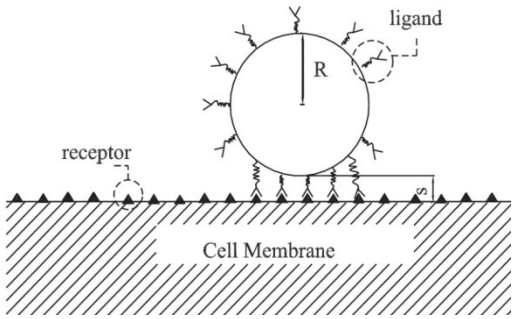
Shaw *et al.* PNAS **May 27, 2008** vol. 105 no. 21 **7387–7392**



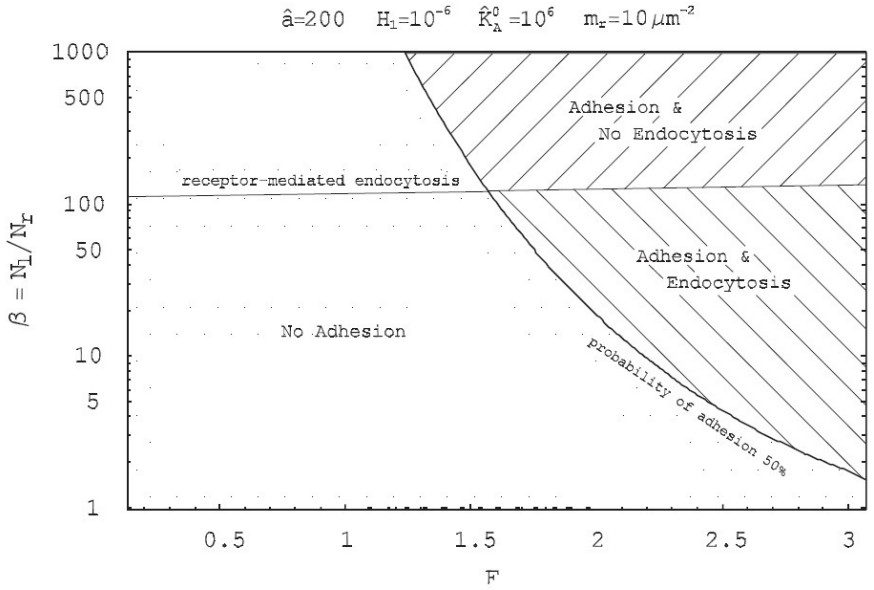
Fourches D, Pu D, Tassa C, Weissleder R, Shaw SY, Mumper RJ, Tropsha A. Quantitative nanostructureactivity relationship modeling. *ACS Nano* 2010, 4:5703–5712.

Mathematical modeling





P. Decuzzi, M. Ferrari Biomaterials 29 (2008) 377–384



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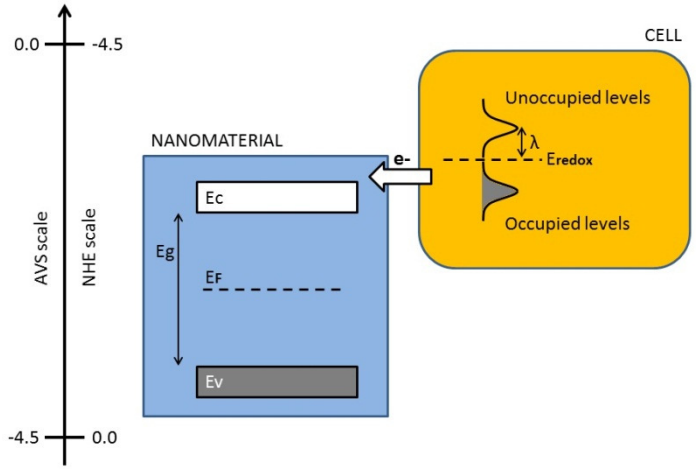
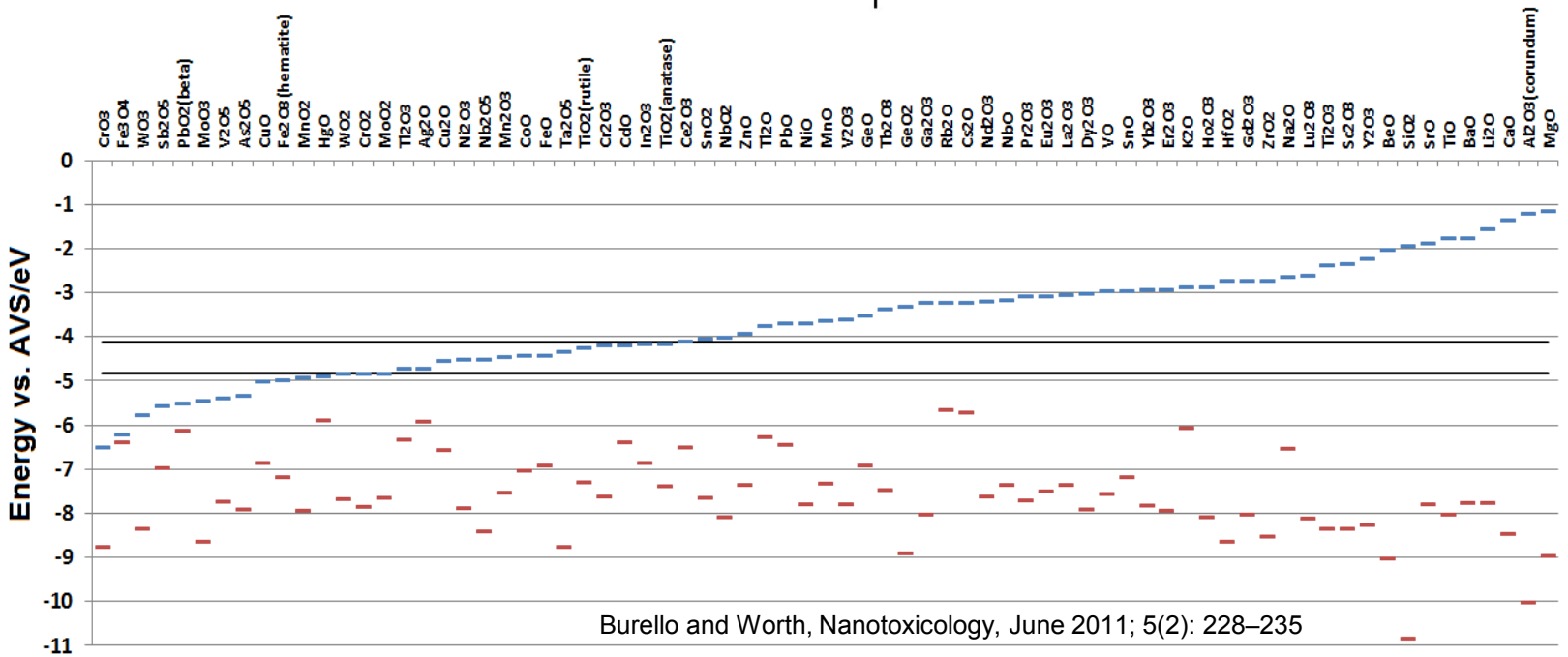
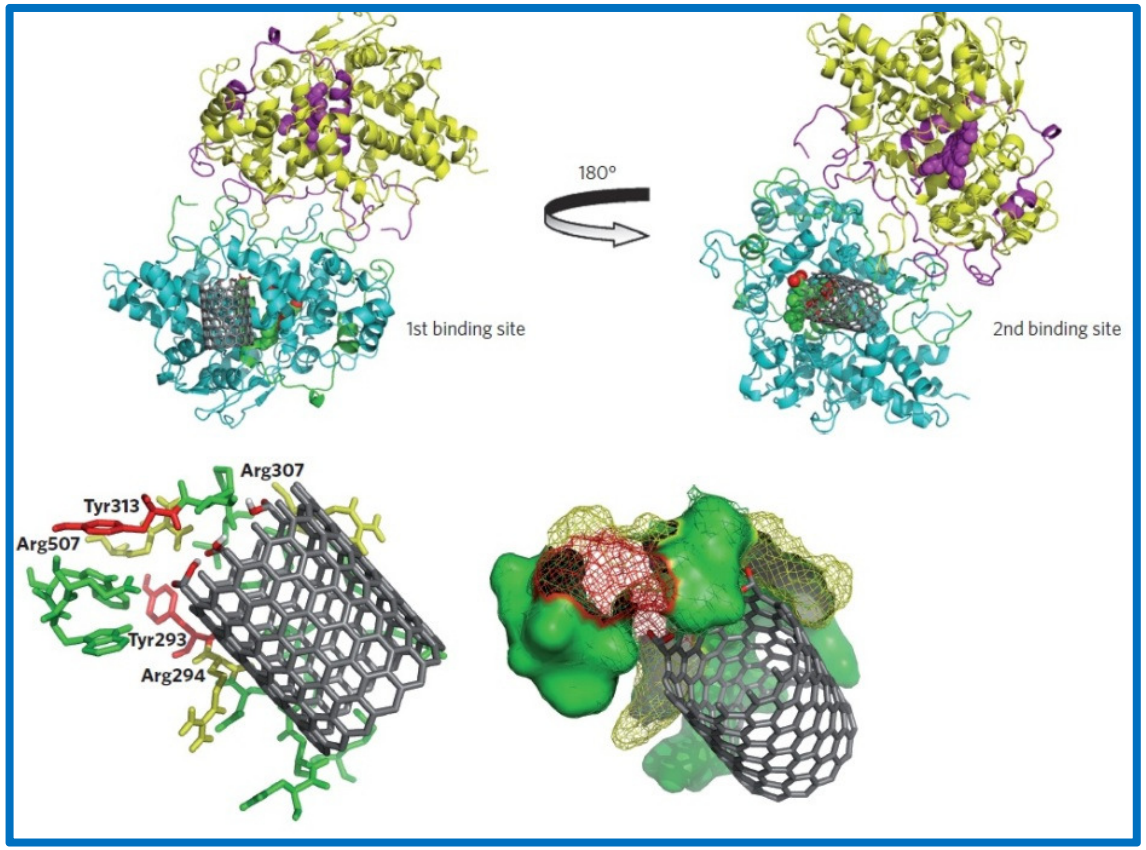
Mechanistically-based models





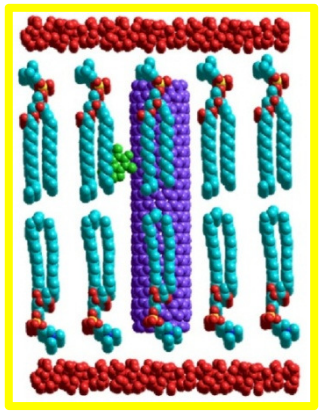
Burello and Worth, Nanotoxicology, June 2011; 5(2): 228–235

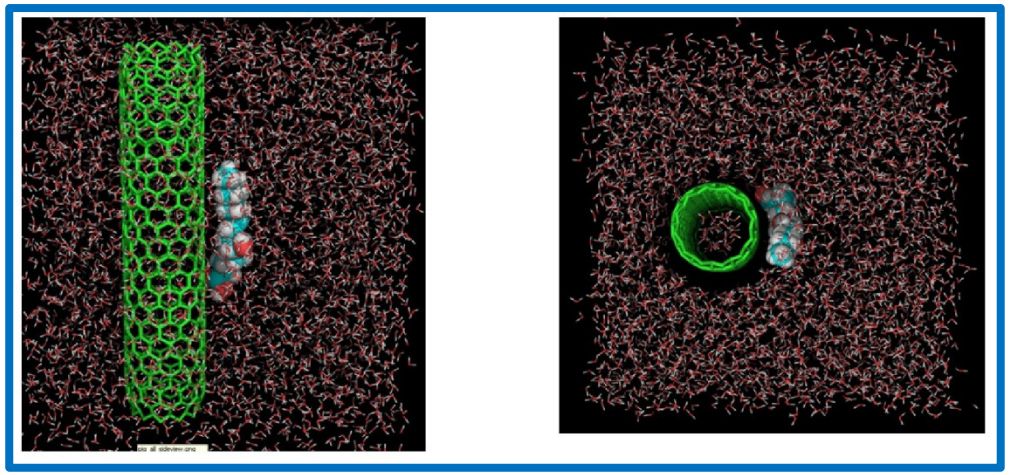
Molecular modeling and simulations - docking

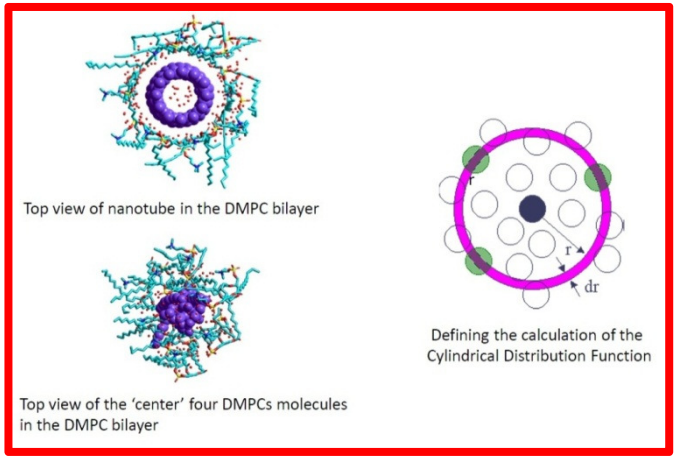


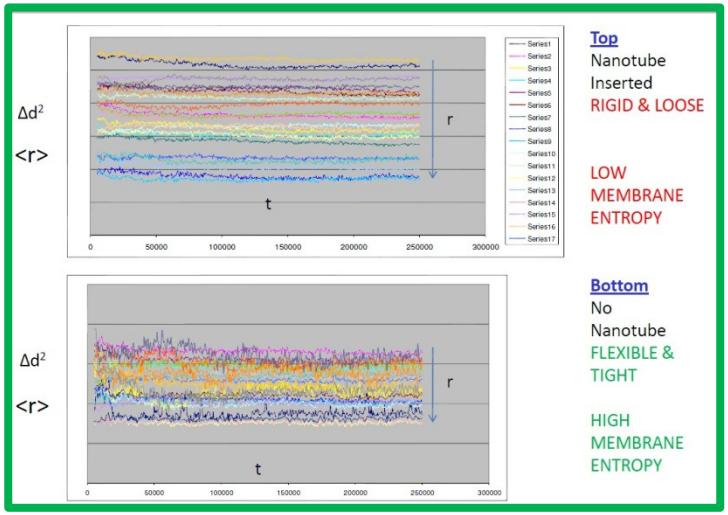
Kagan VE, Konduru NV, Feng W, Allen BL, Conroy J, Volkov Y, Vlasova II, Belikova NA, Yanamala N, Kapralov A, et al. Carbon nanotubes degraded by neutrophil myeloperoxidase induce less pulmonary inflammation. Nature Nanotech 2010, 5:354–359.

Molecular modeling and simulations - molecular dynamics



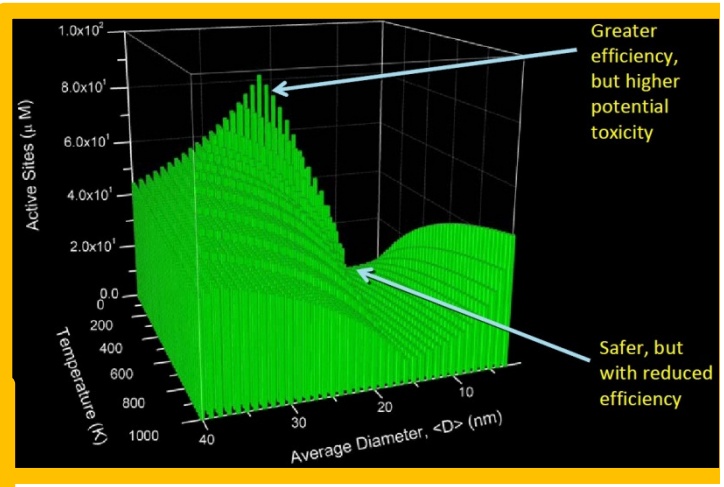


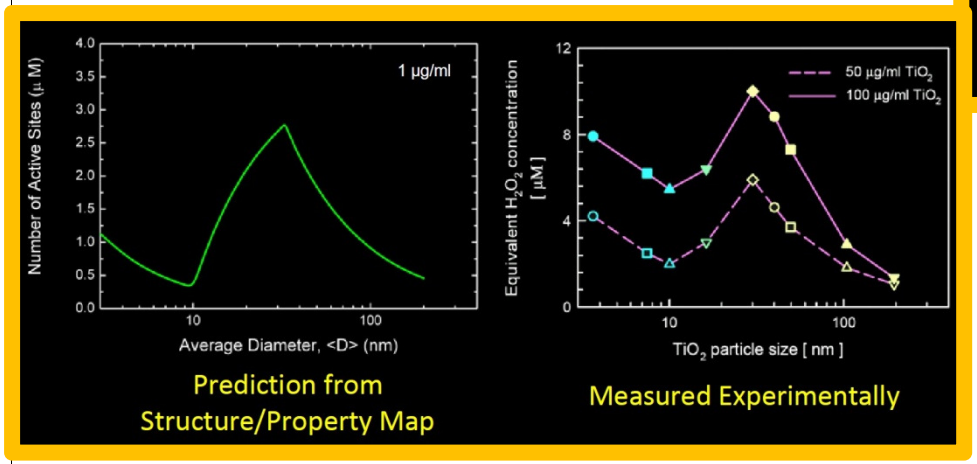




A. J. Hopfinger, et al., J. Chem. Res. Tox., 21, 459-468 (2008).
A. J. Hopfinger, et al., Mol. Pharmaceutics, 6, 873-882 (2009).

Molecular modeling and simulations – thermodynamic cartography





A. S. Barnard, *Energy & Enviro. Sci*. 4 (2011) 539

J. Jiang, G. Oberdöoster, E. Elder, R. Gelein, P. Mercer and P. Biswas, *Nanotoxicology*, 2 (2008) 33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QSPRs – 1

$$\log k_i = c + rR_i + p\pi_i + a\alpha_i + b\beta_i + vV_i \quad i = 1, 2, 3, \ldots, n$$

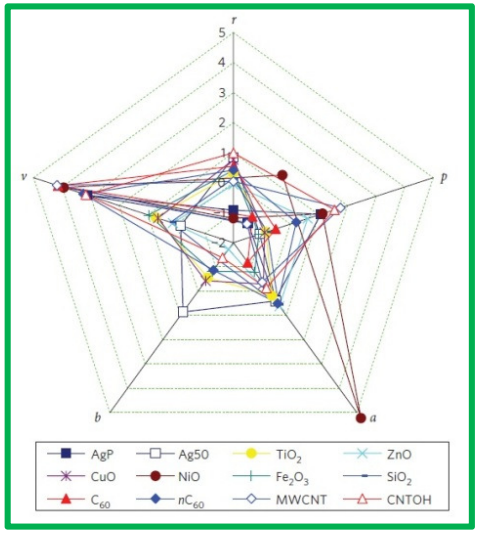
N=28 diverse compounds ranging from alcohols to different hydrocarbons)

R_i is the excess molar refraction representing the molecular force of lone-pair electrons
π_i is the effective solute dipolarity and polarizability,
α_i is the effective solute hydrogen-bond acidity
β_i is the effective solute hydrogenbond basicity
V_i is the McGowan characteristic volume that represents London dispersion.

The regression coefficients [r, p, a, b, v] are the nanodescriptors to be derived from the regression analysis

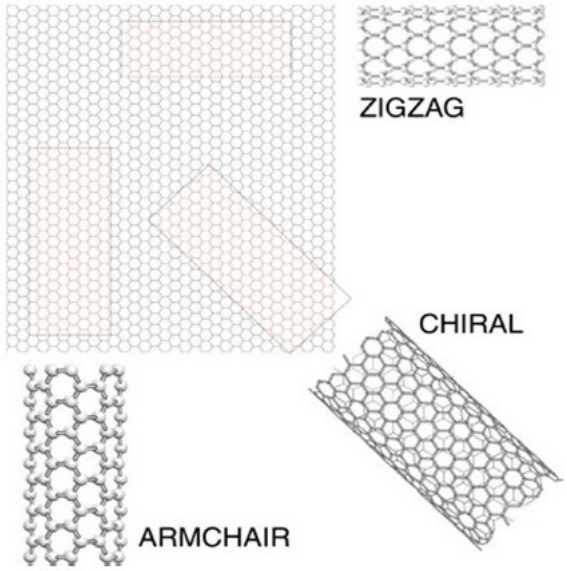
Predicted log *k* values of steroid hormones on MWCNTs.

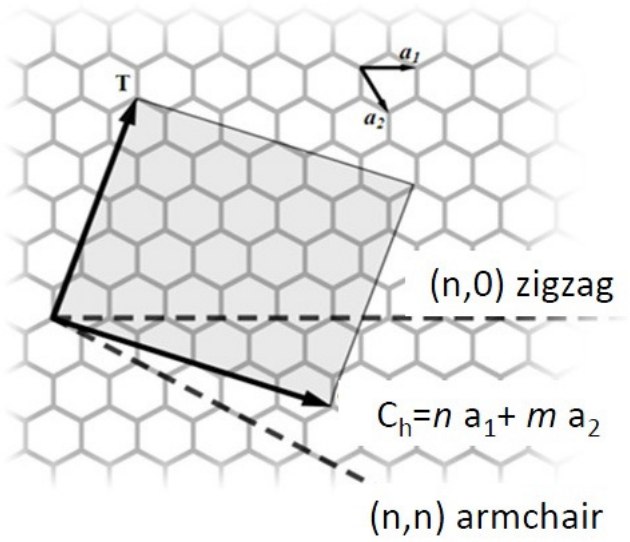
Hormone	*R*	*π*	*α*	*β*	*V*	Predicted log *k*
Testosterone	1.55	2.27	0.31	1.01	2.383	9.75
Progesterone	1.56	2.49	0	1.04	2.622	11.2
Oestradiol	1.85	2.3	0.81	0.95	2.199	9.02
Hydrocortisone	2.04	2.92	0.73	1.9	2.798	10.0
Aldosterone	2.13	3.35	0.48	1.91	2.755	10.7
L-thyroxin	4.14	2.83	1.03	1.31	3.071	12.6
Ethinyl oestradiol	2.07	2.43	0.9	1.02	2.395	9.85



Xin-Rui Xia et al. DOI: 10.1038/NNANO.2010.164

QSPRs – 2





Log K_{OW} = -3.92 + 3.77 n - 3.60 m

n = 8, R^2 = 0.99, s = 0.37, F = 2.93

n_{test} = 8, R^2_{test} = 0.99

log S_W = -5.10 - 3.51 n - 3.59 m

n = 8, R^2 = 0.99, s=0.05, F 126

n_{test} = 8, R^2_{test} = 0.99

Toropov, Leszczynska, Leszczynski (2007) *Comput. Biol. Chem.* 31: 127-128.


Discussion

- 1. Structure definition:
  - - from spectra
  - - modeling
- 2. Descriptors:
  - - form experimental data (e.g. spectra)
  - - computational tools
- 3. Experimental data
  - - HTS/DoE
- 4. Intrinsic Vs. Extrinsic properties
- 5. Broader context
  - - SD (integrate functionality with safety)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Thank you for your attention!