A Joint Workshop 2012 eu-us bridging nanoEHS research efforts

25-26 OCTOBER 2012, HELSINKI, FINLAND

Predictive Modeling for Human Health

US-EU Workshop 2012

EU co-chair: Prof. Bengt Fadeel

US co-chair: Prof. Yoram Cohen

www.us-eu.org

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- Predictive Modeling
- The session will focus on quantitative structure-activity relationship (QSAR) modelling to understand and predict toxicological effects of nanomaterials
- Speakers: Dr. Yoram Cohen, UCLA; and Dr. Enrico Burello, TNO, The Netherlands

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- 1st TC in Predictive Modeling CoR:

- Three themes were emphasized: *correlation* [between *in vivo* and *in vitro* studies, between high-throughput results on cell lines and organisms, between physico-chemical properties and human hazard], *modeling*, and *new approaches*

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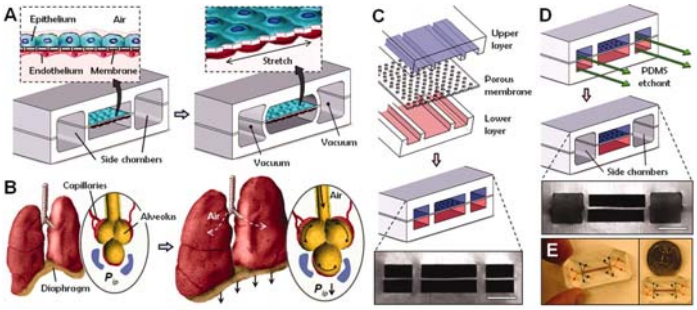
- 1st TC in Predictive Modeling CoR:

- *Modeling*: physiologically-based pharmacokinetic (PBPK) and Quantitative Structure-Activity Relationships (QSARs)
- *New approaches*: bioinformatics and/or systems biology processing, and implementation of new model organisms

Science AAAS

Model systems for in vitro testing of nanomaterial toxicity: biomimetic "lung-on-a-chip" microsystem



- The lung mimic revealed that cyclic mechanical strain accentuates toxic and **inflammatory responses to silica nanoparticles** (Huh et al., Reconstituting organ-level lung functions on a chip. Science. 2010 Jun 25;328(5986):1662-8).

Pessimistic view: after over a decade of research, answers for the most basic questions are still lacking

- "After over a decade of research, **answers for the most basic questions are still lacking**: the data is either not there, or inconsistent because experimental approaches vary from paper to paper making it impossible to compare results. More **coherence in the experimental methods and materials** used, and a clearer set of research priorities are needed in nanotoxicology."
- Schrurs & Lison, Nat Nanotech. 2012 Sep;7(9):546-8.

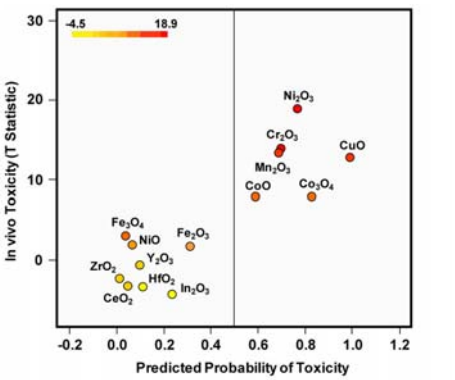
Optimistic view: use of a predictive toxicological approach and high-throughput screening (HTS)

- "We define a predictive toxicological approach as the use of mechanisms-based **high-throughput screening *in vitro* to make predictions** about the physico-chemical properties of nanomaterials that may lead to the disease outcomes *in vivo*. The *in vivo* results are used to validate and improve the *in vitro* HTS and to establish structure-activity relationships that allow **hazard ranking and modeling** by an appropriate combination of *in vitro* and *in vivo* testing."
- Nel et al. Acc Chem Res. 2012 Jun 7. [Epub ahead of print].

ACSNANO

Predictive approach: use of metal oxide nanoparticle band gap to develop a predictive toxicological paradigm

- Zhang et al. (2012) show that it is possible to use **conduction band energy [E(c)] levels** to determine the toxicological potential of 24 metal oxide nanoparticles at cellular (in vitro) and animal (in vivo) level
- While the toxicity of CuO and ZnO is not predicted by E(c) levels, the adverse effects of these nanoparticles could be explained by their solubility, and the release of toxic metal ions

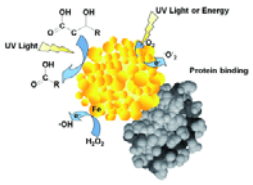


[Zhang et al. ACS-NANO. 2012 May 22;6(5):4349-68]

[Fadeel et al., Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2012]

Understanding the toxicological propertise of engineered nanomaterials: the synthetic versus the biological identity

- Recent research suggests that the **corona of biomolecules** determines the ”biological identity” of engineered nanoparticles; hence, a thorough characterization of the ”synthetic identity” (physico-chemical properties) and the ”biological identity” is essential for the development of safe nanomaterials



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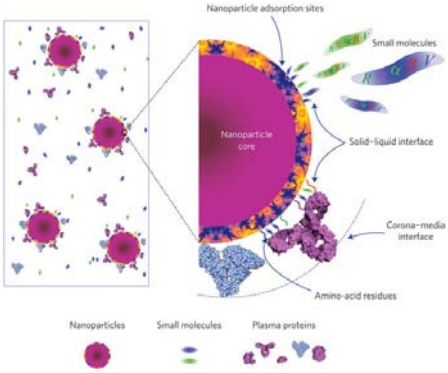
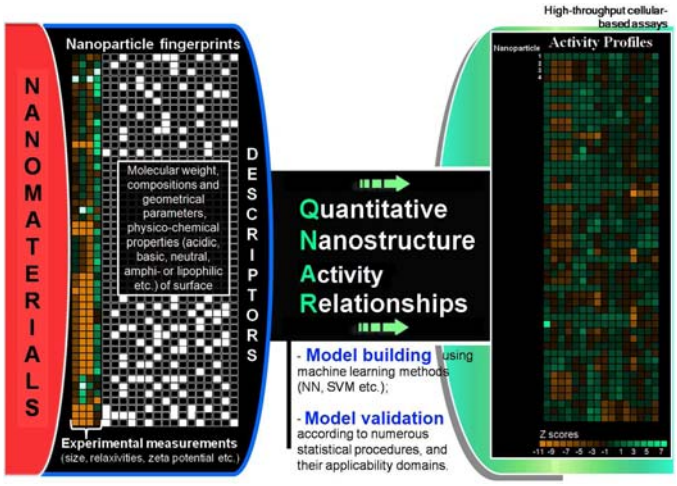
Biological surface adsorption index to predict nanomaterial interactions with biological systems

- The formation of nanoparticle-protein coronas is governed by **molecular interactions** between chemical groups on the NP surfaces and the amino acid residues of the proteins
- Xia et al. have suggested a **biological surface adsorption index** based on the quantification of the competitive adsorption of a set of small molecule probes onto the nanoparticles



[Xia XR, Monteiro-Riviere NA, Riviere JE, Nat Nanotechnol. 2010;5(9):671-5]

Predictive modeling: structure–activity relationship modeling using both calculated and experimentally measured properties of nanoparticles as descriptors



[Fourches et al. ACS-NANO. 2010 Oct 26;4(10):5703-12]

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- Dr. Yoram Cohen, UCLA, USA
- Dr. Enrico Burello, TNO, The Netherlands

- Rapporteur:
- Dr. Lang Tran, IOM, UK