Mining a Nanoparticle Dataset, Compiled Within the MODENA-COST Action

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ABSTRACT

Engineered nanomaterials (ENM) have new or enhanced physico-chemical properties compared to their micron-sized counterparts, but may also have an increased toxic potential. Animal and in vitro testing are typically employed to investigate the toxic effects of (nano)materials. The sheer number of ENMs and their physico-chemical parameters make it impossible to only use in vivo and in vitro testing, and modelling technologies are also deployed to find relationships between ENM parameters and toxicity. A heterogenous dataset containing information on 192 nanoparticle endpoints was compiled within the MODENA COST-Action consortium. Here, the available data was mined to identify relationships between nanoparticle properties and cell-death as measured with four cytotoxicity assays. ANOVA, collinearity analyses and classification and regression trees gave indications on potential relations between the NP-properties and toxicity, but could not deliver a robust model. More information and datapoints are necessary to build well-validated models.

KEYWORDS
Cytotoxicity, Datamining, In Silico Modelling, In Vitro Assays, Nanoparticles, Physico-Chemical Parameters, QSAR

INTRODUCTION

According to the EU commission (2011) a ‘nanomaterial (NM)’ means “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm.” These materials display different properties compared to the conventional variants of the bulk materials, because nanoparticles (NPs) have a greater surface area per weight due to their small size (Ehret et al., 2014). Based on these different properties, they find new applications in very diverse domains, ranging from medical and pharmaceutical industry (e.g., vaccine delivery, cancer therapy), cosmetics applications (sunblock oil), to environmental applications (e.g. breaking down oil with tungsten oxide nanoparticles), applications in electronics (e.g., silver nanoparticle ink to form conductive lines in circuit boards), energy (e.g., silicon nanoparticles coating of anodes of lithium-ion batteries to increase battery power and reduce recharge time). Although there is an enormous interest in different applications of NPs, it is seen that nowadays companies are more reserved to use or to publish research concerning these materials (European Nanotechnology Landscape Report, 2011). This restraint is based on a lack of information concerning the (non)safety of the particles and the associated negative public information that induce a certain lack of faith in these nanomaterials.

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As engineered nanomaterials (ENM) have new or enhanced physico-chemical properties in comparison to their micron-sized counterparts, their properties also make ENMs potentially dangerous, and several reports have been published describing potential deleterious effects of NMs on humans, for example, the observation that both multi-walled and single-walled carbon nanotubes cause platelet aggregation and vascular thrombosis acceleration (Radomska et al., 2005) and induction of ROS-stress and DNA damage in lymphocytes by nano-TiO$_2$ (Kang et al., 2008).

Due to the high number and heterogeneity of NP samples and experimental systems, it is difficult to find common principles of NP toxicity. More sophisticated NPs will make safety evaluations even more complicated (Hartung, 2010). It is clear without any doubt, that it becomes necessary to screen NPs for harmful effects and to establish their safe use, but reliable and reproducible screening approaches are needed to test the basic materials as well as nano-enabled products (Nel et al., 2013a). To determine whether the unique chemical and physical properties of NPs result in specific toxicological properties, the nanotechnology community needs new ways of evaluating hazard and ultimately assessing risk. This has been the topic of several workshops, involving multiple stakeholders from academia, government and industry (Nel et al., 2013b; Beaudrie et al., 2014).

Animal studies are the most confirmatory for determining deleterious effects of chemicals and possibly also of NMs (Dong et al., 2014). They are usually implemented during the steps needed to bring new compounds/materials to the market. However, animal studies are costly and labor-intensive and they are therefore not suited to explore the sheer number of potential NM variables that can influence in vivo activity (Shaw et al., 2008). In vivo test systems can also have a limited predictivity for human adverse effects (Shanks et al., 2009) and there is an EU policy to reduce the animal testing. Therefore, several major initiatives have begun to utilize in vitro methods to determine the biological activities (including toxicity) of NPs and to characterize the nanostructure-dependent properties (Oberdörster et al., 2005; Periasamy et al., 2014; Ding et al., 2014) and a variety of new technologies have emerged to develop in vitro signatures predictive for in vivo response.

In addition to in vitro testing, chemoinformatics methods such as Quantitative Structure-Activity Relationship (QSAR) modelling have also been applied to establish statistically significant relationships between measured biological activity profiles of NPs and their physical, chemical and geometrical properties (either measured experimentally or computed from the structure of NPs). This approach has been termed Quantitative Nanostructure-Activity Relationship (QNAR) and Quantitative Nanostructure-Toxicity Relationship (QNTR) modelling, and the potential of QNAR/QNTR models for predicting biological activity/toxicity profiles of novel NMs and for prioritizing the design and manufacturing of NMs towards better and safer products, was demonstrated (Fourches et al., 2010; Luan et al., 2014).

Still, in order to develop ENMs that are safe-by-design, a better understanding of the relationship between the ENM structure and biological activity/toxicity is needed. Based on scientific insights (based on in vivo, in vitro testing and on better physico-chemical characterisation technologies), QNAR/QNTR computational modelling techniques may provide an effective alternative to experimental testing since it enables the prediction of (eco-) toxicological effects based on ENM structure only (Oksel et al., 2015).

The MODENA COST Initiative (www.modena-cost.eu) brought together expertise of NM-scientists, (eco-)toxicologists, and modellers from academia, regulatory agencies and industry to promote inter-disciplinary collaborations with the ultimate aim of producing QNTR-models for ENM. The creation of transparent, validated and rigorous QNTR tools in the field of nanotoxicology according to OECD principles is important for regulatory purposes.

The MODENA scientific program was divided in 3 working groups which were focused on the major disciplines related to the development and use of QNTR: Physical Chemistry (WG1), (Eco)-Toxicology (WG2) and Modelling (WG3). WG3 was responsible for activities on identifying and quantifying the relationship between ENM properties and the biological responses using the pertinent physico-chemical descriptors.
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