Trading in vivo for in silico—a new approach to nanotoxicity assessment

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Prof. Robert Rallo, coordinator of the MODERN project, discusses the initiative's new approach to nanotoxicty assessment, which could help move us towards the wider adoption of in silico methods.

The MODERN project has set out to better understand how nanoparticles affect environmental and human health. Their new approach, which relies on novel computational methods to characterise the structure of nanoparticles and in silico models to assess their effects, also promises to reduce the need for in vivo testing.

Historically, market pressure has often resulted in scientific innovation being made available to consumers even before we were fully aware of its ins and outs. This was notably the case with asbestos, and the same scenario could very well be repeating with nanotechnology if proper safety assessment studies are not conducted and political measures taken accordingly: according to some of the latest forecasts, the nanotechnology market will grow to reach US 75.8 (EUR 65.8) billion by 2020. And while engineered nanoparticles (eNPs) are already widespread in the likes of cosmetics, paint and electronics, we still don't know much about their possible long term effects on biological systems.

To gain a better understanding, scientists still rely heavily on animal testing—in spite of efforts from animal protection activists, scientists and policy makers to put the focus on alternative testing methods. In line with the EU's efforts to implement appropriate testing strategies and with a view to overcoming the current obstacles to a wider adoption of in

silico methods, Prof. Robert Rallo, coordinator of MODERN, initiated the MODERN project in January 2013.

A couple of months before the end of the project, he tells us about its achievements and expected impact on eNP toxicity assessment methods.

Would you say enough is being done in Europe to measure the toxicity of eNPs, before they are put on the market?

In recent years the EU has initiated a significant effort aimed to define the scientific and methodological principles for in vitro and in vivo testing of nanomaterials. Although specific regulations regarding the use of nanotechnology-enabled products are still lacking, the EU is on its way toward providing a basis for the implementation of appropriate testing strategies that will support risk assessment and regulatory decision-making.

The diversity of nanomaterials (e.g., diverse combinations of chemical composition, core-shell structure, shape, functionalization) makes the exhaustive testing of nanomaterials a daunting task. In this context, the development and validation of high throughput screening methods together with the implementation of in silico tools (like the ones developed in MODERN and in other FP7 NMP modeling projects) will contribute in the near future to providing alternative testing methods suitable for the evaluation of a large number of nanomaterials in an efficient and cost-effective manner.

Why does eNP toxicity assessment rely so much on animal testing?

The main reason is that current in vitro assays and in silico tools are not

yet accepted as reliable model systems for nanomaterial toxicity. Dealing with "biological noise" (i.e., data variability) in in vitro high-throughput assays is one of the most urgent challenges to be addressed. In addition there is an equally urgent need of developing large databases of high quality experimental data for the development and validation of in silico toxicity prediction tools.

How do you intend to fill this gap?

At MODERN we are developing in silico tools for nanotoxicity assessment by using different types of information about nanoparticles. The project follows an integrated approach that combines different types of information within the framework of specific Adverse Outcome Pathways. Specifically we focus on nanotoxicity effects driven by oxidative stress responses. We have developed novel methodologies for the calculation of size-dependent nanodescriptors using quantum chemistry and molecular modelling approaches, as well as nano-(Q)SAR based on the descriptors developed for a number of ecotoxicity endpoints in different species, including protozoa, algae and bacteria.

Another achievement is the development of a novel normalization methodology for omics data that is useful to unveil gene and pathway activity at low concentration (i.e., in realistic environmental exposure conditions). Models for predicting nanoparticle cell interactions based on the composition of the nanoparticle's protein corona have also been developed and validated. Finally, we are trying to increase the accuracy of current models by identifying homogeneous categories of nanoparticles and developing new local models for each specific category.

Do the models you developed meet your initial expectations?

We have shown that the integration of different types of information (e.g., physico-chemical properties, structural features and bioactivity profiles at different levels of biological organization) regarding nanoparticles' effects is fundamental for the development of in silico tools suitable for risk assessment of nanomaterials and decision-making.

Since computational models can guide the design of new nanoparticles with controlled toxicity, in silico tools can also be applied for safe-by-design nanomaterials. However there is still a significant lack of (public) information about nanoparticle's toxicity enabling models to be properly assessed and their applicability domain expanded. As a consequence, current models can only be used as preliminary screening tools that provide an indication of the potential adverse effects of a nanomaterial. Further in vitro (and possibly in vivo) testing will be necessary to confirm whether or not a given nanoparticle has toxicity implications.

Would you tend to agree with scientists saying it's impossible to completely stop using animal testing when it comes to ENP toxicity assessment?

Presently the answer is yes. In vivo testing will be necessary to ensure the safety of nanotechnology-enabled products, especially for those nanoparticles used in medical applications. However, the development of more robust in vitro assays combined with in silico predictive tools will have the potential to contribute to a significant reduction in the number of animals used for testing.

In the near future, with the continuous increase in computing power and with improved understanding of the nano-bio interaction mechanisms, I am confident that we will be able to perform accurate simulations of the interactions between nanoparticles and biological systems that will have the potential to completely replace animal testing.

What would you say are the most important things you have learned from your research so far?

The first and most important lesson is that our understanding and modelling capacity for nanotoxicity is still far from what we have for chemical toxicity. There is still a significant lack of knowledge regarding nanotoxicity mechanisms and modes of action. Also, the amount of data available for model development—and more importantly, for model validation—is very limited when compared to the data available for chemicals.

There are still many challenges that hinder the development of in silico nanotoxicity screening tools, and the limited amount of data is just one of the limiting factors. Among others, current important needs include the development of a nomenclature to describe nanomaterials unambiguously; standardised protocols for nanotoxicity testing; protocols for high-throughput screening assays and their associated data preprocessing methodologies in order to generate enough data to enrich and improve current in silico models; and methods for hazard ranking, risk assessment and decision-making.

What do you still need to achieve before the project ends in December?

We are currently evaluating the predictive capacity of the quantum chemistry and molecular modeling descriptors for the metal oxide nanoparticles we developed so far. The computational methods to generate the nanodescriptors are also being refined to incorporate structural changes such as metal doping. In parallel we are using information obtained from nanoparticle categorization to develop ensemble nanotoxicity models based on a collection of locally tuned nano-QSARs. The information provided by these models will then be

used at a final stage to provide hazard ranking and preliminary risk assessment tools for nanomaterials.

More information: For further information, please visit MODERN project website: modern-fp7.biocenit.cat/

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