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Opinion

Nanotoxicity and *In Vitro* Methods: Advantages and Challenges

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Nanomaterials (NM) are defined as engineered structures whose diameter in at least one dimension is less than 100 nm. Nanotechnology is rapidly advancing and is considered one of the most important approaches of the 21st century promising revolution in different fields, such as healthy and food sciences, cosmetics, diagnostic tools and electronics [1]. Therefore, the adverse effects of NM exposure is a growing concern both academically and socially; however, several challenges are encountered as, currently, no clear regulatory guidelines on the evaluation of nano-based materials are available [2]. In this context, the toxicity of different NMs has been extensively studied by using varied non-standard approaches, being the *in vitro* toxicological studies extremely relevant and important.

The *in vitro* procedures display many advantages over the *in vivo* methods. The ease and high-throughput of *in vitro* tests emphasize their potential for use in risk assessment of chemicals and particles. They would allow the testing of numerous materials at different concentrations and on cells from different origins, reduce the effect of inter-experimental variation, and make substantial savings in time and cost [3]. Moreover, they would help the scientific community to improve the understanding regarding the mechanisms of action of the different types of NMs as a function of their main physicochemical characteristics. Because of these significant features, the *in vitro* assays are widely used to screen potential therapeutic compounds for adverse biological effects before *in vivo* testing, thereby reducing the use of research animals, being in agreement with ethical concerns [4].

The development and validation of new *in vitro* methods for screening of the effects of NMs is a huge and expensive task. Therefore, different researchers worldwide are studying the application of the already existing validated methods, developed for chemicals, for the toxicological studies of NMs [5].

The tests already performed revealed that many of the basic toxicological principals in the existing OECD guidelines are applicable to NM testing, even though nano-specific considerations must be made in some aspects.

It is worthy mentioning that NM behavior can differ from conventional chemicals in terms of particle size and kinetics, NM dissolution, aggregation/agglomeration, and surface affinity. Thus, while many *in vitro* assays have been found to provide accurate data for cytotoxicity studies of classic small molecule, they have sometimes proven to be not very reliable when assessing NMs [6,7]. Researchers worldwide have reported conflicting outcomes when *in vitro* and *in vivo* study results are compared, suggesting that more physiologically representative *in vitro* models might be required to minimize reliance on animal testing. Therefore, the suitability of each test for nano-based materials should be properly evidenced by experimental data. Indeed, many authors have been recommended that the NM risk assessment and screening-level decision must be based in the combination of multiple alternative non-animal tests [8]. Besides the classical *in vitro* methods, different approaches have been successfully used to assess the potential toxicity of NMs: (i) 3D *in vitro* skin models for the evaluation of NMs designed for topical use, which can lead to further successful outcomes in nanotoxicology [9]; (ii) Virtual Cell Based

Assay (VCBA), which estimates time-dependent concentration of a test chemical in the cell and cell culture for a given *in vitro* system by using differential equations [10].

Overall, it can be concluded that the development of standard protocols to assess the toxicity of NMs is a very difficult task. Thus, it is firstly important to identify the knowledge gaps toward improvements for experimental and strategy design. Then, it is needed to represent realistic exposure scenarios and to consider NM-specific concerns such as characterization and assay interferences. The *in vitro* methods are not perfect or much better than *in vivo* methods at all; however, it is clear that there are global appeals to develop reliable alternatives to animal testing.

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