Nanotoxicology for safe development of nanomaterials: light and shadows

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The nanotech tsunami of engineered nanomaterials (NM) raises the issue of their impact on environmental and human health, being more and more widespread in industrial and biomedical applications, as well as in everyday life. Since emerging evidence that even at the cellular level NM behave differently from the corresponding bulk materials, the protection of public health, consumers and workers in this sector is now a topic of enormous interest that is taken into serious consideration by the competent authorities in charge in environmental and health safety. In this context, it is a decade since nanotoxicology is recognized as a sub-discipline of toxicology with the aim of: obtaining information on adverse effects of NM and the possible ways of contact with humans and the ecosystem; developing appropriate research guidelines; providing a scientific basis to reduce the uncertainty of the risk assessment. Unfortunately, although hazard assessment of NM has made a significant progress, the nanotoxicology has not produced the desired results in terms of scientific knowledge relevant for the risk assessment. This is mainly due to a poor collaboration/communication between the various projects, despite a substantial EU Framework Programme funding in this matter. In particular, although in the last decade some biological effects of NM have been documented we still lack a fundamental understanding about modes of action and mechanisms leading to toxicity and aspects of biokinetics and its impact on toxicity. Moreover, significant uncertainties on methodological framework (incomplete physicochemical characterization, unrealistic doses, different biological models, absence of validated methods) and vague and fragmentary data on NM in consumer products equalize the nanotoxicology to a "fishing trip in the sea of uncertainty", making difficult to support research and regulation.

Herein we discuss: (i) the biological effects of NM as emerged from nanotoxicology research by *in vivo* and *in vitro* biological models (ii) key factors concerning the modes of action of NM in relation to their toxicity (physicochemical characterization, interaction with biological fluids, uptake, intracellular trafficking); (iii) concerns about the potential risk as consequence of human exposure to nanoparticles via food and cosmetics; (iv) strategic priorities for future nanotoxicology research, i.e. its evolution from being an observational into a predictive discipline. In this context, the crucial need is to clarify NM toxicity pathways which lead to understanding the molecular fundamentals in groups of NM with marked similarities. This in order to include the mechanistic knowledge in the technology development, to help in the safe design of new NM, and to be into the development of a rational testing approach. In addition, most of the current nanotoxicology research deals with the 1st generation NM. However, 2nd and 3rd generation NM will appear soon on markets and appropriate testing for such NM should be developed.

Nanotoxicology must keep away from two extremes: on one side, to generate superficial information to draw the attention of the media or the public, or to arouse distrust towards nanotechnology for ideological but not scientific reasons; on the other side, to remain silent in front of the conduct of industrial operators more interested in marketing consumer products that have not received the necessary controls. In this context, only a close cooperation between producers, users and researchers in the area of nanosafety will lead to a sustainable and safe development of nanotechnology. In any

case, nanotoxicology will play a central role in prevention science if it can give a sound scientific basis and establish itself in the global context as a responsible and independent discipline.