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Biomarkers of susceptibility: State of the art and implications for occupational exposure to engineered nanomaterials

Ivo Iavicoli [a,*], Veruscka Leso [b], Paul A. Schulte [c]

[a] Department of Public Health, Division of Occupational Medicine, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy
[b] Institute of Public Health, Section of Occupational Medicine, Catholic University of the Sacred Heart, Largo Francesco Vito 1, 00168 Rome, Italy
[c] National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 4676 Columbia Parkway, MS C-14, Cincinnati, OH 45226, USA

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ABSTRACT

Rapid advances and applications in nanotechnology are expected to result in increasing occupational exposure to nano-sized materials whose health impacts are still not completely understood. Scientific efforts are required to identify hazards from nanomaterials and define risks and precautionary management strategies for exposed workers. In this scenario, the definition of susceptible populations, which may be at increased risk of adverse effects may be important for risk assessment and management. The aim of this review is to critically examine available literature to provide a comprehensive overview on susceptibility aspects potentially affecting heterogeneous responses to nanomaterials workplace exposure. Genetic, genotoxic and epigenetic alterations induced by nanomaterials in experimental studies were assessed with respect to their possible function as determinants of susceptibility. Additionally, the role of host factors, i.e. age, gender, and pathological conditions, potentially affecting nanomaterial toxicokinetic and health impacts, were also analysed.
Overall, this review provides useful information to obtain insights into the nanomaterial mode of action in order to identify potentially sensitive, specific susceptibility biomarkers to be validated in occupational settings and addressed in risk assessment processes. The findings of this review are also important to guide future research into a deeper characterization of nanomaterial susceptibility in order to define adequate risk communication strategies. Ultimately, identification and use of susceptibility factors in workplace settings has both scientific and ethical issues that need addressing.

1. Introduction

Rapid advances in nanotechnology worldwide are leading to a massive production and application of engineered nanomaterials in consumer products. As a consequence, an increasing number of workers are expected to become exposed to nanomaterials, while the potential health and safety impacts are still unknown (Iavicoli et al., 2014; Schulte et al., 2014). Therefore, efforts to actively anticipate potential hazards of nanomaterials and to define risks and preventive needs for exposed workers have become necessary (Schulte and Trout, 2011; Trout and Schulte, 2010). In this context, precautionary risk management may be enhanced by defining susceptible populations which develop adverse effects from nanomaterial exposure due to the lack of capacity, beyond the limits of human variability, to tolerate or respond effectively to these potential exogenous toxicants (Manno et al., 2010). Moreover, the need to define susceptible populations to nanomaterials, has been motivated by recent epidemiologic findings reporting that ultrafine particles can contribute to adverse respiratory and cardiovascular effects resulting in morbidity and mortality, particularly, in susceptible parts of the population (Oberdörster et al., 2005; Penttinen et al., 2001; Peters et al., 1997a, 1997b; von Klot et al., 2002).

Evidence indicates that inherited and acquired genetic susceptibility, epigenetic modifications as well as alterations in physiological structures and functions induced by age, pathological conditions, and lifestyle factors, may lead to different phenotypic expressions from xenobiotic exposures. Particularly, inherited genetic susceptibility may play a role in influencing the individual response to exogenous exposures in a complex "gene–environment" interaction (Hunter, 2005). Therefore, understanding which genetic polymorphisms, genotoxic changes, epigenetic profiles and host factors may affect

Abbreviations: Ag, silver; AhR, aryl-hydrocarbon-receptor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATM, ataxia telangiectasia mutated protein kinase; ATR, ataxia telangiectasia and Rad3-related protein kinase; Au, gold; CdTe-QDs, cadmium telluride quantum dots; $CoFe_2O_4$, cobalt ferrite; CYP450, cytochrome P450; Ercc-2, excision repair cross-complementing rodent repair deficiency complementation group 2; Fe_2O_3, iron(III) oxide; Fe_3O_4, iron(II,III) oxide; GST, glutathione transferase; IC50, half maximal inhibitory concentration; MW-CNTs, multi-walled carbon nanotubes; NP, nanoparticle; OGG1, 8-OhdG-DNA glycosylase 1; PARP-1, poly (ADP-ribose)polymerases-1; PEG, polyethylene glycol; ROS, reactive oxygen species; Si, silica; SiO_2, silicon dioxide; SW-CNTs, single walled-carbon nanotubes; TiO_2, titanium dioxide; Xpa, xeroderma pigmentosum group A protein complex.

* Corresponding author.
E-mail addresses: ivo.iavicoli@unina.it (I. Iavicoli), veruscka@email.it (V. Leso), pas4@cdc.gov (P.A. Schulte).

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the toxicokinetic and dynamic nanoparticle (NP) modelling, appear essential to get insights into the still not understood NP exposure/disease continuum and to identify susceptibility biomarkers indicative of an elevated sensitivity to NP effects. This seems an even more challenging issue considering that the same great variability in NP physicochemical properties, i.e. in terms of size, chemical composition and surface area, that make them so attractive for a variety of product applications may also prove complex and changeable exposure scenarios, potentially influencing individual response to NP toxicity. Therefore, the aim of this review was to critically assess experimental studies addressing susceptibility aspects, potentially affecting the health impact of NP exposure, in order to identify possible susceptibility biomarkers to be further studied and validated in occupational populations exposed to nanomaterials. These biological indicators may be useful to provide quantitative estimates of a population variability to be employed into an adequate occupational NP risk assessment and consequently in the plan of specific or implemented workplace preventive and protective measures. This information could also possibly be used in deriving occupational exposure limits. Overall, this information may give stimulus to innovative research intended to contribute to a more comprehensive, effective assessment and management of potential NP risks in occupational settings.

2. Materials and methods

A bibliographic search of scientific databases including PubMed, ISI web of Science and Scopus was conducted to identify experimental studies addressing susceptibility aspects potentially affecting individual responses to nanomaterial exposure published up to September 2015. We carried out a preliminary search for the terms "nanomaterials" to assess the exposure context, and "susceptibility factors" as the outcome of the research, combined with the operator "AND". The authors, independently examined all titles and abstracts retrieved and selected articles that met the inclusion criteria. These included peer-reviewed *in vitro*, *in vivo* and human studies published in English and exploring aspects potentially affecting the health impact of engineered nanomaterial exposure. Exclusion criteria were applied for studies not focusing on the topic of research. The preliminary search retrieved 45 references through PubMed, 8 results through ISI web of Science and 9 via Scopus database. Out of these, after the exclusion of studies that did not met the inclusion criteria and removal of duplicates, only 3 were considered suitable for our scope by title and abstract screening. Therefore, we extended our research including the following keywords as free terms in the electronic search: "nanomaterial exposure", "nanoparticle exposure", which were individually combined with the operator "AND" with the terms related to the major subject of "factors involved in susceptibility to adverse health effects" such as "genotype", "genetic polymorphisms", "metabolic enzymes", "CYP450", "DNA repair systems", "epigenetic*", "age", "gender", "pathological conditions", "susceptible population". All full texts of the papers considered valuable for the aim of our review were obtained and a critical evaluation performed. The citation pool of relevant publications identified in the literature search was further supplemented through the manual assessment of the reference list accompanying published papers for other potentially eligible articles. Overall, our search retrieved a total of 69 publications for review.

3. Results

The following paragraphs will present a critical review of the available literature to provide a comprehensive view on the NP susceptibility issue with a specific focus on those aspects that emerged as potentially influencing the individual variability to tolerate or respond to such xenobiotics.

3.1. Inherited genetic variability and nanomaterials

Inherited genetic variabilities, including polymorphisms, that may affect individual susceptibility to NP exposure are still unknown. Genotype is responsible for recognition and responses to xenobiotics and, consequently, relative susceptibility to induced health effects. To date, information on heritable genome alterations able to influence the individual susceptibility to adverse health effects resulting from NP exposure are not directly available. Particularly, genetic polymorphisms that can alter the activities of enzymes involved in xenobiotic activation/detoxification reactions have not been investigated, although they may be prime candidates for identifying susceptibility biomarkers due to their capability to cause diverse responses to chemical insults. Additionally, the role of genetic variants in genes involved in DNA damage repair pathways, as determinants of susceptibility to nanomaterial insults, has not been explored. However, this topic merits wider investigation in order to define variants useful as potential biomarkers of NP susceptibility. This seems important considering that an affected capacity to repair the DNA damage may be associated with a variable risk of disease due to genome instability directly contributing to human pathologies and tumorigenesis (Tuteja and Tuteja, 2001). This lack of information is probably due to the limited knowledge regarding the NP toxicokinetic and dynamic behaviour, and particularly on the role of the above mentioned enzymes in NP metabolism as well as on their protective action against potential NP induced genotoxic effects. Moreover, the multitude of still unexplored pathways potentially involved in NP adverse effects, as well as the lack of information concerning the presence of physiological factors that may offset the effects of potential genetic variants currently prevent reaching definite conclusions regarding possible genetic susceptibility factors.

3.2. Nanomaterials and metabolic pathways

Alterations induced by nanomaterials in biological systems, generally involved in xenobiotic metabolism, may affect the individual susceptibility to adverse health effects. In this context, available toxicogenomic data, concerning gene, protein, and metabolite expression changes induced by NPs in pathways responsible for the metabolism of the vast majority of exogenous substances existing in occupational and general living environments may provide advantageous information. This may be helpful to understand NP modes of action and to explicate core biological processes affected by nanomaterials or possibly involved in their toxico-dynamic behaviour to identify potential parameters of individual susceptibility. In this context, it should be taken into account that most of the studies in this review did not compare the susceptibility to nanomaterials with that to particles characterized by the same chemical composition but larger size since these investigations were more generally conducted to probe mechanism and identify response. Moreover, from the perspective of a possible "drug–drug" interactions, it is worth noting that metabolic alterations induced by nanomaterials may result in antagonistic, synergistic and additive "mixture" of effects, modifying toxicities induced by co-exposed substances and thus disease susceptibilities. The next section focuses on the alterations induced by NP exposure in the expression and functionality of metabolic enzymes. These changes may provide data to guide the future identification of potential NP susceptibility factors. Finally, it is important to recognize that the metabolism of xenobiotics is a complex process and while individual factors may be identified multiple factors and systems may be required to affect susceptibility.

3.2.1. Nanomaterial induced alterations on phase I and II metabolic enzymes

Several *in vitro* and *in vivo* studies demonstrated that NPs were able to induce alterations in biotransformation phase I and II enzymatic pathways. In humans, in fact, biotransformation of xenobiotics occurs by a two stage process involving the functional group oxidation, exerted