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NEWS AND OPINIONS

A strategy for grouping of nanomaterials based on key physico-chemical descriptors as a basis for safer-by-design NMs

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Summary There is an urgent need to establish a fundamental understanding of the mechanisms of nanomaterial (NM) interaction with living systems and the environment, in order for regulation of NMs to keep pace with their increasing industrial application. Identification of critical properties (physicochemical descriptors) that confer the ability to induce harm in biological systems is crucial, enabling both prediction of impacts from related NMs (via quantitative nanostructure—activity relationships (QNARs) and read-across approaches) and development of strategies to ensure these features are avoided or minimised in NM production in the future (''safety by design''). A number of challenges to successful implementation of such a strategy exist, including: (i) the lack of widely available systematically varied libraries of NMs to enable generation of sufficiently robust datasets for development and validation of QNARs; (ii) the fact that many physicochemical properties of pristine NMs are inter-related and thus cannot be varied systematically in isolation from others (e.g. increasing surface charge may impact on hydrophobicity, or changing the shape of a NM may introduce defects or alter the atomic configuration of the surface); and (iii) the effect of ageing, transformation and biomolecule coating of NMs under environmental or biological conditions.

A novel approach to identify interlinked physicochemical properties, and on this basis identify overarching descriptors (axes or principle components) which can be used to correlate with toxicity is proposed. An example of the approach is provided, using three principle components

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which we suggest can be utilised to fully describe each NM, these being the *intrinsic* (inherent) properties of the NM, *composition* (which we propose as a separate parameter) and *extrinsic* properties (interaction with media, molecular coronas etc.).

A nanomaterial (NMs) is any substance that has the defining feature of one or more dimensions in the nanoscale, described for regulatory purposes in the European Union (EU) and by the US Environmental Protection Agency as being 1 < NM < 100. Many forms of NMs are simply smaller sizes of existing particulate materials, e.g. nanosilica and nanotitania, while others are purpose-built to exploit quantum effects that occur due to size-induced confinement. It is not yet clear, however, whether size is a sufficient descriptor to correlate with toxicity, or whether size is simply an amplifier of effects resulting from chemical composition and increased 'strain', via, for example, an increased reactivity or rate of dissolution resulting from a larger surface area to volume ratio at smaller size.

There have been multiple suggestions regarding how to classify and prioritise NMs for safety assessment, including classification based on (i) commercial importance and volume of production [1]; (ii) composition/chemistry (e.g. metals, metal oxides, carbon-based, polymeric etc.); (iii) dimensionality/shape/morphology (e.g. ISO [2]); (iv) complexity/functionality, from legacy NMs through so-called 2nd—4th generation NMs [3]; (v) modes of action [4], similar biopersistence/biokinetics [5,6] and/or parameters with a proven link to toxicological or biological response(s), i.e. the adverse outcome pathways concept as the basis of QNARs [7]; or (vi) *synthetic and biological identity*, whereby, in addition to describing the composition (the ''synthetic identity''), a ''biological'' property is used to describe the NMs as they exist in the exposure context [8—10], and following uptake by organisms where localisation in lysosomes and proteolytic digestion of the corona biomolecules is the likely fate [11,12]. The biological identity thus incorporates corona composition (identity of proteins, lipids etc.) and evolution, as well as any protein folding/unfolding and impacts on receptor binding and signalling pathways, and how these could be correlated with uptake, localisation and impact in different cells and tissues, although significant additional research is needed to demonstrate this effectively [13—17].

Primary physicochemical descriptors of NMs may not be the most appropriate to predict their toxicological behaviour, in part as many of these are ''context dependent'', i.e. are affected by the surrounding matrix (pH, ionic strength, biomolecules or macromolecules etc.), the route of exposure, etc. Additionally, many NM properties are inter-dependent such that changing one property may inadvertently result in change to several others, e.g. changing NM shape/length may cause surface defects or change the surface chemistry [18—21]. This makes development of systematically varied libraries of NMs difficult, where individual properties are varied in a precise manner to allow identification of key parameters driving toxicity, and to facilitate identification of toxicity thresholds for different descriptors as well as development of QNARs. There is growing awareness that NMs age and are transformed throughout their lifecycle [22,23], further adding to the challenge of predicting their toxicity. While some context-dependent physico-chemical property changes are obvious and well documented, e.g. size and surface charge alterations as a result of biomolecule binding, others such as redox or photochemical activity are less obvious and require experimental assessment and verification. Such so-called secondary or derived features, including the potential of NMs to generate reactive oxygen species (ROS) or release toxic metal ions, have been suggested as potentially more relevant characteristics for some toxicological outcomes [24].

An important step towards demonstrating the feasibility of grouping of NMs based on combinations of related physicochemical properties is described by Sayes et al. [25]. Using principle component analysis (PCA) applied to measurable NM features (engineered size, concentration, agglomerated size in water, zeta potential, pH and age of the suspension, and oxidant production) for five metal colloids (silver, copper, nickel, zinc and iron), a seemingly homogeneous group of NMs could be separated into sub-groups depending on interdependencies observed in their nanodescriptors [25]. PCA has also been applied to metabolomics data following earthworm exposure to TiO_2 NMs [26], and to reducing complexity of slurry [27] and aerosol particle size distributions [28].

Four main principles or modes of action for NM toxicity are currently recognised:

(i) the release of toxic chemical constituents from NMs (e.g. Cd from quantum dots, ionic silver from Ag NPs) — i.e. *NM dissolution*;
(ii) direct effects from physical contact with NMs, influenced by their size, shape and surface properties, and which produce interferences with important biological functions for example by altering conformation of biomolecules — i.e. *NM surface effects*;
(iii) the inherent properties of the material, such as photochemical and redox properties resulting from bandgap or crystalline form — i.e. *NM structure effects*; and
(iv) the capacity of NMs to act as vectors for the transport of other toxic chemicals to sensitive tissues — i.e. *NM Trojan horse effects*.

Once a NM encounters an organism/cell, toxicity could occur through one or a combination of these mechanisms.

Building on the concepts outlined above, of interlinked descriptors and the potential for PCA to identify those descriptors most closely correlated with toxicity or adverse outcomes, we present a hypothesis that NM toxicity can be predicted as the sum of three ''quantifiable'' parameters (principle components) that capture the diversity of potential modes of action. As a starting point, we propose three principle components (PCs), namely:

- *intrinsic* properties which are inherent to the nano-form of a material, and include e.g. structure and structural strain. A number of NM physicochemical properties map onto the *intrinsic* axis, including shape, porosity, structural configuration and bandgap.
- *extrinsic* properties which are those connected to the surface area of the NM, including e.g. surface interactions and transformations of NM surface and biomolecules (e.g. unfolding, receptor activation, membrane damage, fibrillation etc.) as a result of binding.
- *composition* aspects such as inherent molecular toxicity, charge, hydrophobicity and coating (although also linked to both the intrinsic and extrinsic axes).

Clearly, each of these PCs will have multiple contributors, and the relative contribution of these will vary for different NMs and will need to be teased out as part of the overall quantification of each PC. A key feature of this approach is that it allows separation of modes of action e.g. dissolution is primarily associated with specific NM compositions, but can be facilitated by certain intrinsic properties such as a high strain conformation associated with, for example, non-spherical structures such as needles or nano-stars, and by extrinsic factors such as strongly binding ligands. Thus, we envisage utilisation of a set of scales from low to high for each of the three parameters: in each scale, low is correlated with low toxicity and high with high toxicity.

We expect that this approach will enable development of QNARs and facilitate the grouping of NMs on the basis of where they sit in this 3-dimensional space, as well as facilitate regulatory decision-making. The fact that the same physico-chemical descriptor can contribute to more than one of the PCs is a key feature of this approach: the major physico-chemical descriptors driving toxicity, as described by ITS-NANO [29] for example, can be explicitly determined from the weight of contribution to each PC/axis (i.e. the loadings), as can the main mode of action as this will be the PC accounting for the highest amount of the variability in the data, as shown schematically in Fig. 1.

The role of *intrinsic* (structural) and *extrinsic* (surface and interface with media) properties has only recently begun to emerge in the context of nanotoxicity descriptors; the relative significance of these two groups of properties, as well as internal scaling are yet to be established. It has, however, been recently demonstrated that the effect of structural strain can become a major descriptor of toxicity [21,30]. While it has long been known that quartz (crystalline) silica is more toxic than amorphous silica owing

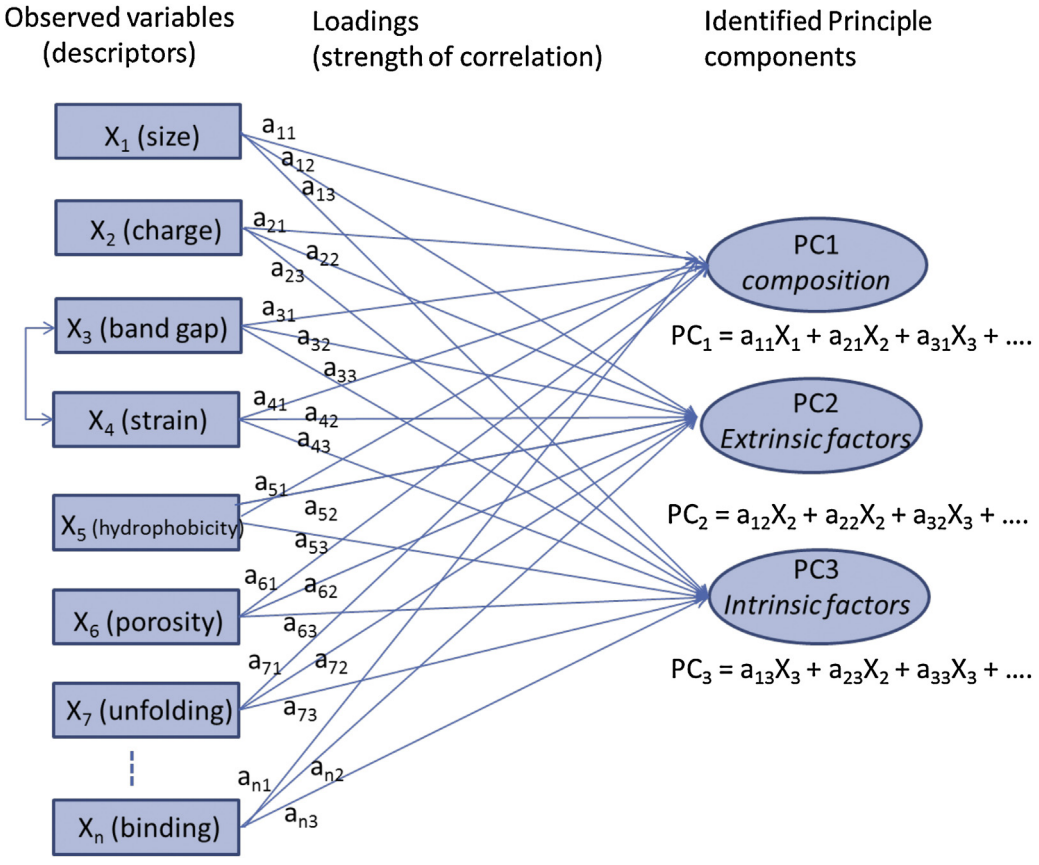

Figure 1 Schematic illustration of the use of PCA as applied to determination of the primary descriptors of NMs toxicity. Initially, each of the variables (measured end-points) are considered to be equal, and using latent variable analysis the approach determines the principle components (PCs) and how much of the total variance in the starting dataset is described by each PC. Interdependence of descriptors, or indeed of PCs can also be accounted for, represented by double-headed arrows between the interrelated entities (e.g. arrow between band-gap and strain for example) and the degree of inter-dependence is also calculated. Some connections are non-intuitive and may prove not to exist, but the benefit of the approach is that it allows all potential correlations to be tested.

to its biopersistence [31], it is increasingly emerging that crystallinity may not be a pre-requisite for acute silica toxicity, with amorphous variants such as ''vitreous silica'', the common product of rapid solidification of any molten silica, and high-temperature flame pyrolysis or so-called fumed or pyrolytic silica also emerging as toxic [21,32—34]. Other sources of structural strain include surface curvature, compositional modification (doping), angular or needle-like structures, faceting and potentially porosity.

This opinion article is intended to stimulate discussion and ideas regarding approaches to grouping of NMs on the basis of their likely toxicity and mode of action, and suggests a way forward that encompasses the current state of knowledge and builds upon it in a systematic manner. Toxicity itself is multi-parametric, with numerous possible end-point measurements (e.g. inflammation, cell death, DNA damage, changes in metabolome, transcriptome, proteome, etc.) reflecting multiple modes of action, and the elegance of the PCA and related latent variable model approach is that for each toxicity end-point the PCs (physico-chemical characteristics, biological interactions etc.) contributing to this can be identified, allowing comparison across toxicity end-points and establishment of QNARs. PCA thus has the potential to provide a simple yet robust framework for nano(eco)toxicological classification to underpin both understanding and legislation for nanosafety.

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