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Multiscale Coupling Strategy for Nano Ecotoxicology Prediction

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The number of toxicological studies characterizing hazards posed by manufactured nanoparticles (NPs) has increased in recent years. Identification of both the mode of action as well as the mechanism of toxic action of NPs have become areas of significant concern. A controversy is centered on the notion on which intrinsic chemical and physical characteristic of NPs considerably contributes to adverse effects. In order to reduce the need for expensive and time-consuming experimental testing, predictive models are being developed to investigate the relationships between the intrinsic properties of NPs and their biological impacts.[1] The calculation of descriptors reflecting intrinsic NP properties has been complicated by the structural complexity and the dynamic behavior of NPs.[2] In particular, there is a lack of studies comparing the environmental toxicity of NPs to human toxicity results. Issues concerning quantum chemical properties and aqueous dispersion stability can have important consequences for quantitative nanostructure−activity (ecotoxicity) relationships (termed as nano-QSA$_{(eco)}$Rs). It is therefore important to develop suitable descriptors for predicting the aquatic toxicity of NPs.[3]

We propose that a multiscale analysis could comprehensively strengthen the understanding of toxicity mechanisms and could efficiently couple multiscale descriptors to forecast apparent toxicity of NPs to aquatic organisms. The multiscale system refers to the different scales microscopic (atomic), nanoscopic, mesoscopic, and macroscopic scales (Figure 1) that need to be understood and described in model descriptors. The quantum aspects of chemical reactions that can induce an adverse effect may be central for predicting the toxicity of NPs. Currently, on the microscopic scale, quantum mechanics methods have become the core of simulation techniques. Quantum chemical calculations can also be used to obtain descriptors such as total energy, orbital energy, and thermodynamic parameters from nanocrystal lattices or nanoclusters. The enthalpy of formation of a gaseous cation as an index of the chemical stability of metal oxide NPs has been successfully applied to predict the cytotoxicity of the NPs.[1] Compared to metal oxide NPs, prediction toxicity models for carbon-based NPs based on quantum chemistry-based descriptors are currently relatively scarce. A reason for this lack of research may be related to the diversity of carbon nanostructures with different dimensionalities (0D, 1D, 2D, 3D) and hybridization states (sp, sp2, sp3) of constituent carbon atoms.

Due to their large specific surface area, by definition NPs hold a strong tendency of agglomeration to lower their free energy. Many interaction forces exist between nanocarbons, including van der Waal's attraction and $\pi-\pi$ stacking, with occasional electrostatic interaction, hydrogen bonding, and hydrophobic interaction. These interaction forces have provided essential opportunities for spontaneous assembly.[4] Thus, NPs have a strong tendency of aggregation/agglomeration, which influences their toxic effects. We therefore suggest to predict the toxicity of nanocarbons using quantum chemical descriptors (e.g., potential energy) to describe the interaction forces.

In addition, many nanocarbons are photosensitized and can produce phototoxicity to aquatic organisms. The gap between the highest occupied molecular orbital and the lowest unoccupied molecular orbital was proposed as a qualitative indication of the potential photoinduced toxicity of polycyclic aromatic hydrocarbons (PAHs) to aquatic organisms.[5] PAHs are generally regarded as precursors of carbon-based nanomaterials. We therefore suggest that nano-QSA$_{(eco)}$R models incorporating orbital energy descriptors can be applied to predict the aquatic phototoxicity of nanocarbons.

On the nanoscopic scale (Figure 1), structural descriptors have been used to describe the three-dimensional size, shape, and surface properties of NPs. Hazard assessments of NPs

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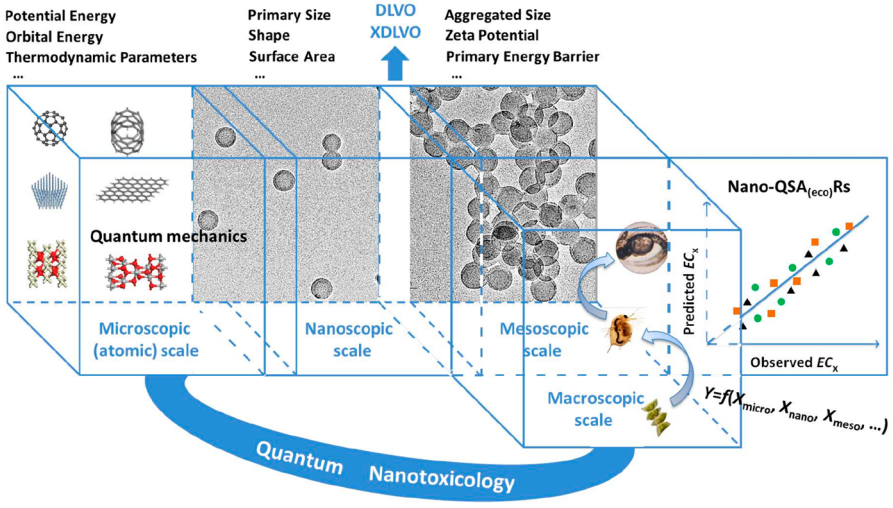

Figure 1. Three-dimensional construction of multiscale coupling strategy for nano ecotoxicology prediction

currently focus on the effects that NP-structural descriptors have on the environmental behavior and toxicity of the particles. Due to particle surface modifications (e.g., coating) and various environmental factors (e.g., pH, ionic strength, and dissolved organic carbon), aggregation/agglomeration and the dispersion state of NPs can be altered.[6] In view of specific interactions between NPs and organisms, the bioavailable fraction of NPs is likely to be proportional to the concentration of "free" NPs, with aggregates/agglomerates functioning as a source for "free" particles. Apart from increasing our understanding of biological response interpretations, the stability of NPs in an aqueous medium is also an important factor determining the aquatic toxicity of NPs. Moreover, it is the interplay of multiple structural descriptors, such as size and zeta potential, that allows NPs to cause toxic effects. Issues in aquatic toxicology of NPs therefore require a transfer from the nanoscopic scale to the mesoscopic scale (Figure 1). To address this conversion, mesoscopic simulation based on classical Derjaguin−Landau−Verwey−Overbeek (DLVO) theory or extended DLVO (XDLVO) theory mechanism can be applied. In order to describe NP aggregation/agglomeration and dispersion in aqueous suspensions, DLVO or XDLVO theory combines the structural descriptors of NPs with typical environmental factors and surface modification factors. The primary energy barrier (indicating NP stability) of particles derived from the interaction energy profiles based on DLVO or XDLVO theory can be used as a mesoscopic descriptor which can be implemented for assessing the aquatic toxicity of NPs.

On the macroscopic scale (Figure 1), the apparent toxicity of NPs to aquatic organisms is usually expressed as the concentration of a compound provoking x % (e.g., x = 1, 5, 10, 50) effect (EC_x). The apparent EC_x value as an end point for aquatic toxicity is a well-suited and relatively easily accessible end point for development of nano-$QSA_{(eco)}$Rs.

With this understanding, we synthesized the issues relating to the prediction of aquatic toxicity of NPs across three dimensions, and we propose the following recommendations for further scientific actions: (1) Quantum chemical descriptors obtained on the microscopic (atomic) scale should be an integral part of nano-$QSA_{(eco)}$Rs. Availability of a larger number of quantum chemical descriptors that are indicative of the toxicity of NPs may mark the development of quantum nanotoxicology; (2) We need to turn the nanoscopic insights toward the prediction of aquatic toxicity to the mesoscopic insights, as the interplay of multiple structural descriptors favors the mesoscopic simulation; (3) The primary energy barrier as a mesoscopic descriptor derived from the colloidal theory should be integrated into future development of nano-$QSA_{(eco)}$Rs, as aqueous dispersion stability associated with NP-NP interactions plays a pivotal role in explaining toxicity.

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The authors declare no competing financial interest.

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