Modelling the interactions of advanced micro- and nanoparticles with novel entities

Zhang, F.

Summary

With the rapid development and intensification of society and economy, novel entities such as engineered nanoparticles (ENPs), microplastics (MPs), nanoplastics (NPs), and viral particles are emerging. These novel entities may pose risks to humans and to the environment. Micro- and nanoparticles (MNPs) can adsorb other novel entities to form aggregated contamination, due to their small particle size and relative large surface area. In this thesis, we used advanced computational methods including molecular simulation, data mining, machine learning (ML), and quantitative structure-activity relationship (QSAR) modeling. These methods were used to investigate the mechanisms of interaction between MNPs and other novel entities (**chapters 2 and 3**), the joint toxic action of MNPs and other novel entities, the factors affecting their joint toxicity to ecological species (**chapter 4**), as well as to quantitatively predict the interaction forces between MNPs and other novel entities (**chapters 2 and 3**), and the toxicity of their mixtures (**chapters 5 and 6**).

In **chapter 2**, we have investigated the molecular interactions between carbon nanoparticles (CNPs) and the SARS-CoV-2 RNA fragment using molecular mechanics simulations to tackle some mechanistic issues related to the impact of ENPs on SARS-CoV-2. The interaction affinity between the CNPs and the SARS-CoV-2 RNA fragment increased in the order of fullerenes < graphenes < carbon nanotubes. Furthermore, we developed QSAR models to determine the interactions of 17 different types of CNPs from three dimensions with the SARS-CoV-2 RNA fragment. The QSAR models on the

interaction energies of CNPs with the SARS-CoV-2 RNA fragment show high goodness-of-fit and robustness. Molecular weight, surface area, and the sum of degrees of every carbon atom were found to be the primary structural descriptors of CNPs determining the interactions. Within this chapter a theoretical insight into the adsorption/separation and inactivation of SARS-CoV-2 was provided. The results allow to design novel ENPs which interact efficiently with the genetic materials of SARS-CoV-2. This contributes to minimizing the challenge of time-consuming and labor-intensive experiments with viruses under high risk of infection, whilst meeting our precautionary demand for options to handle any new versions of the coronavirus that might emerge in the future.

In **chapter 3**, we have used molecular dynamic simulations to investigate the molecular interactions between five MPs and the SARS-CoV-2 RNA fragment at temperatures ranging from 223 to 310 K in vacuum and in water to determine the mechanisms underlying the impact of MPs on SARS-CoV-2. Furthermore, we have compared the interactions of the SARS-CoV-2 RNA fragment with the MPs to the performance of the RNA fragments of SARS-CoV-1 and Hepatitis B virus interacting with the MPs. The interaction affinity between the MPs and the SARS-CoV-2 RNA fragment was found to be greater than the affinity between the MPs and the RNA fragments of SARS-CoV-1 or Hepatitis B virus, independent of the environmental media, temperature, and type of MPs. The mechanisms of the interaction between the MPs and the SARS-CoV-2 RNA fragment involve electrostatic and hydrophobic processes, and the interaction affinity was associated with the inherent structural parameters of the MPs monomers. The results presented in this chapter indicate that

humans are exposed to MPs via their lungs, and the strong interaction with the gene materials of SARS-CoV-2 likely affects the exposure of humans to SARS-CoV-2.

In **chapter 4**, we have applied data mining methods to understand the joint impacts of multiple ENPs and predict the toxicity of mixtures of ENPs. Accordingly, we have collected and categorized the toxicity of mixtures of ENPs to a variety of different species, covering algae, bacteria, daphnia, fish, fungi, insects, and plants. Using co-occurrence networks, it was revealed that 53 % of the cases with specific joint response showed antagonistic, 25 % synergistic, and 22 % additive effects. The combination of nCuO and nZnO exhibited the strongest interactions in each type of joint interaction. Compared with other species, plants exposed to multiple ENPs were more likely to experience antagonistic effects. The main factors influencing the joint response type of the mixtures were 1) the chemical composition of individual components in mixtures, 2) the stability of suspensions of mixed ENPs, 3) the type and trophic level of the individual organisms tested, 4) the biological level of organization (population, communities, ecosystems), 5) the exposure concentrations and time, 6) the endpoint of toxicity, and 7) the abiotic field conditions (e.g., pH, ionic strength, natural organic matter). Ultimately this knowledge constitutes the first building blocks that allow to build a computational approach able to reduce the experimental costs of ecotoxicity testing of mixtures of ENPs of varying composition, and including both nanohybrids as well as mixtures of different ENPs.

In **chapter 5**, we proposed computational toxicity approaches with classical mixture equations to quantitatively predict the joint toxicity of emerging or untested/unknown mixtures of multiple ENPs.

Research priorities for the prediction of the toxicity of mixtures of ENPs are identified and we suggest to systematically sort out the toxicity and ecotoxicity information of ENPs gathered into "databases". Moreover, expected and/or actual environmental concentrations of ENPs need to be obtained to be implemented for actual risk profiling of various combinations of ENPs in the environment. These environmental concentrations can be further used for the estimation of ratios of the individual particles present in mixtures of ENPs, and then the weighted descriptors of ENP mixtures can be evaluated by the mixture ratios. It is essential that information on the mode of toxic action of single ENPs to species is systematically documented. This issue deserves priority in the selection of methods to assess mixture toxicity and the selection of mechanism-based nano-descriptors.

In **chapter 6**, we have combined toxicity data generated in our lab with experimental data reported in the literature to predict the combined toxicity of seven metallic ENPs for *Escherichia coli* at different mixing ratios (22 binary combinations). We thereafter applied two ML techniques, support vector machine (SVM) and neural network (NN), and compared the differences in the ability to predict the combined toxicity by means of ML-based methods and two component-based mixture models: IA and CA. Among 72 developed QSAR models by the ML methods, two SVM-QSAR models and two NN-QSAR models showed good performance. Moreover, an NN-based QSAR model combined with two molecular descriptors, namely enthalpy of formation of a gaseous cation and metal oxide standard molar enthalpy of formation, showed the best predictive power for the internal dataset (R^2_{test} = 0.911, adjusted R^2_{test} = 0.733,

$RMSE_{test}$ = 0.091, and MAE_{test} = 0.067) and for the combination of internal and external datasets (R^2_{test} = 0.908, adjusted R^2_{test} = 0.871, $RMSE_{test}$ = 0.255, and MAE_{test} = 0.181). In addition, the developed QSAR models performed better than the IA and CA models. The estimation of the applicability domain of the selected QSAR models showed that all the binary mixtures in the training and test sets were within the applicability domain. Hence, this work confirms that the models developed can provide a methodological and theoretical basis for the ecological risk assessment of mixtures of ENPs.

The results of this thesis indicate that understanding the mechanisms of interactions between novel entities in the environment and their modes of joint toxic action can provide an important theoretical basis for establishing effective risk assessment procedures to mitigate the effects of novel entities on ecosystems and human health. Furthermore, this thesis provides an important technical support and practical basis for the quantitative prediction of the environmental behavior and toxicological effects of novel entities and their mixtures by applying various advanced *in silico* methods individually or in combination.