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Summary

Nanotechnology is seen as a revolutionary technology which greatly benefits the world economy. However, as usual there is a tension between the need to manufacture new nanomaterials with desired properties, and the need to protect the environment and human beings from the potential risks associated. The lag between the time needed to evaluate the safety of engineered nanomaterials (ENMs) and the rapid development of nanotechnology has already caused concerns about the safe use of ENMs. Assessing the risks of ENMs solely on the basis of experimental assays is time-consuming, resource intensive, and constrained by ethical considerations (such as the principles of the 3Rs of animal testing, i.e. replacement, reduction, and refinement). The adoption of computational toxicology in this field is a high priority. Computational toxicology is able to contribute to the prediction of the extent of toxic effects of untested ENMs, to the hazard categorization and labeling of ENMs, and to the establishment of hazard threshold values that are sufficiently protecting the ecosystem with respect to the ENMs of concern. These three steps are listed by the European Chemicals Agency (ECHA) as the three elements in evaluating the hazards of ENMs. A comprehensive hazard assessment for ENMs is essential for both the risk characterization and the safe-by-design of nanomaterials.

To facilitate the use of computational toxicology in assisting the hazard assessment of ENMs, the research of this thesis started from the integration and evaluation of existing available and accessible data regarding the toxicity of metal-based ENMs to selected organisms (Chapter 2). A database of 886 records was developed, containing information on bacteria, algae, yeast, protozoa, nematode, crustacean, and fish; and on ENMs composed of metals, metal oxides, nanocomposites, and quantum dots. The analysis indicated that Ag ENMs are the most widely studied ENMs, together with TiO₂ and ZnO ENMs. *Daphnia magna, Escherichia coli,* and *Pseudokirchneriella subcapitata* are the most frequently tested species in the database. Biological effects investigated for each group of organism were analyzed, and the types of ENMs and species in the database were described in as much detail as possible. ENMs were classified into different hazard categories adhering to the EU Directive 93/67/EEC.

Following up the data integration and evaluation, the state-of-the-art of the development of (quantitative) structure–activity relationships for ENMs (nano-(Q)SARs) was reviewed in Chapter 3. Issues concerning the sources of data for modeling, existing nano-(Q)SARs, and mechanistic interpretation were discussed
and an outlook on the further development of this field was presented. The analysis showed that cellular uptake of ENMs by different cells and the toxicity to *Escherichia coli* are the main focus of nano-(Q)SAR modeling. Models were developed for both quantitative and categorical predictions of the biological activities of ENMs based on different data mining approaches. As could be concluded from the identified descriptors, lipophilicity and hydrogen bonding capacity of surface modifiers were found to be of most significant importance for the cellular uptake of ENMs. The released ions and generation of oxidative stress are seen as driving factors in causing nanotoxicity in some cases; nano-specific properties such as surface chemistry, size are also believed to play a role. Similar to chapter 2, also here we saw the problem of data scarcity and data quality. The characterization of ENM structures and the consideration of dynamic transformations of ENMs in the exposure medium in modeling should also be carefully handled.

Based on the identified research gaps on nano-(Q)SARs, in Chapter 4 the nano-SARs for the categorization of ENM hazards were built on the basis of the retrieval of existing toxicity data. The global nano-SARs across species in case study I (LC50 data, 320 ENMs in training set and 80 ENMs in test set) and III (MIC data, 133 ENMs in training set and 33 ENMs in test set) yielded reasonable accuracies (above 70%). Species-specific nano-SARs were also constructed for *Danio rerio, Daphnia magna, Pseudokirchneriella subcapitata,* and *Staphylococcus aureus* with high predictability. The molecular polarizability, accessible surface area, and solubility of ENMs were identified in the models that were built as predominantly influencing the toxicity of metallic ENMs. The study contributes to the classification and labeling of metallic ENMs for regulatory purposes.

Once an ENM is classified in one of the hazard classes or categories listed by ECHA, a risk characterization for the ENM is required. This necessitates the derivation of threshold levels for ENMs in order to compare with relevant exposure levels and to quantify associated risks. In case of generic risk assessment, the 5th percentile (HC5) of the species sensitivity distributions (SSDs) is commonly used for this comparison. Chapter 5 therefore focused on the development of SSDs for metallic ENMs with the explicit consideration of the characteristics of ENMs, experimental conditions, and different types of endpoints. Based upon a sufficient number of data entries, separate SSDs could only be built for Ag ENMs based on the characteristics surface coating, size, shape, and exposure duration. Separate SSDs were also developed to determine whether and to what extent the shape of the SSD curve alters and the resulting
HC5s varies based on different toxicity endpoints. As could be concluded from the developed SSDs, the PVP- and sodium citrate coatings were found to enhance the toxicity of Ag ENMs; for Ag ENMs with different size ranges, differences in behavior and/or effects were only observed at high exposure concentrations; the SSDs of Ag ENMs separated by either shape or exposure duration were all nearly identical. Meanwhile, crustaceans were found to be the most vulnerable group to metallic ENMs.

In conclusion, our study has expanded the use of computational toxicology in hazard assessment with regard to the safe handling of ENMs. The results obtained contribute to the integration and evaluation of toxicity data, the identification of research gaps on ENM-related modeling, and the development of nano-SARs and SSDs for metallic ENMs. Despite the uncertainties that are associated with our results, as mainly due to limited data quality and availability, we managed to take this field one step forwards and contribute to better-informed regulatory decisions of ENMs. To enable the next step to be made, it is essential that research in the relevant fields more strictly adhere to the guidance that has been issued regarding proper reporting of scientific data on the fate and effects of ENMs. This will allow for efficient data curation and proper comparison of experimental data.