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Summary of Doctoral Dissertation

Results of conducted research are presented in my doctoral dissertation "**Optimal selection of descriptors for structure-activity modeling of nanoparticles based on causality analysis"**

The objectives of conducted research in the framework of my doctoral dissertation were: (i) development of new structural descriptors for NPs and evaluation of compatibility of the known descriptors as instruments of NP description and (ii) evaluation of the developed models in terms of causality. On this basis I offered three main research hypotheses.

First, statement that the bulk materials may demonstrate constant physical properties regardless of their size or shape are not applicable to the case of nanomaterials. Nanomaterials could demonstrate both size- and shape-dependent properties. Therefore, classic conventional descriptors for quantitative structure-activity are unable to reflect size- and shape-dependent features of nanomaterials.

Existing size-dependent descriptors are derived from experimental data. It makes them sensitive to measurement errors. Other size-dependent descriptors are based on complex and long-term quantum chemical calculations. In this context, I suggested to develop a new simplified size-dependent descriptors.

I have established new size-dependent descriptors, which do not require complex calculations. I have introduced descriptors that are based on the geometric "liquid drop" model. This proposed model was applied to describe different important properties of nanoparticles, such as surface area, surface-to-volume ratio, etc. The new descriptors combine basic physical assumptions with simple geometrical transformations. The role of theoretical descriptors in physicochemical interpretation is in agreement with modern theories of thermal conductivity

Secondly, it is widely known, that the unique properties of nanomaterials are conditioned by different factors, related to the specific organization of nanostructure e.g. NPs release of ions from a surface, huge contact area, aggregation effects, etc. On this basis I suggested, that successful description of properties or mechanisms of action would become possible by means of a hierarchical combination of descriptors. The main idea of hierarchical approach is simultaneous use of a number of descriptors, which reflect the NP structure at different levels of organization: from ions and single molecules to ensemble or aggregate. I have applied several types of molecular descriptors, which reflect nanoparticle structure at different levels of organization. For example, I expressed the basic proprieties of released fraction of metal ions using the known metal–ligand binding theory. Next, I presented molecular formulas of metal oxide NPs as a planar molecular graph, and calculated physicochemical descriptors. It was a first attempt of calculation of the fragmental descriptors for nano-QSAR modeling.

I have developed four nano-(Q)SAR models contained different combinations of mentioned descriptors. It indirectly confirms the fact, that different cells (heathy or malignant) and organisms (prokaryotic and eukaryotic) are damaged by nanoparticles in different ways. Basing on the comparative analysis of developed nano-(Q)SAR, I found that size-dependent descriptors and ionic characteristics are two dominant causes of toxic action. These results are in agreement with known mechanisms of NPs toxicity, and reflect the release of ions and a fraction of available molecules on this surface. Thus, the developed models are successful examples of implementation of the proposed hierarchical approac

Finally, I postulated that relationships between a target property or activity and a descriptor could be characterized by chance correlation. Statistically it was already proven, that statistically reliable relationship does not imply causation. In the field of quantitative-structure activity relationships approach, the deep and reliable interpretation of developed models is possible only for cause-effect relationships. Therefore, verification of the relationships between descriptors and the target activity plays a vital role in QSAR modeling. I suggest, that causal inference methods could support nano-QSAR models as an additional validation criteria, and they would help to interpret the mechanisms of toxicity more precisely.