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From Basic Physics to Mechanisms of Toxicity: “Liquid Drop” Approach Applied to Develop Predictive Classification Models for Toxicity of Metal Oxide Nanoparticles

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Many metal oxide nanoparticles are able to cause persistent stress to live organisms, including humans, when discharged to environment. To understand the mechanism of metal oxides nanoparticles toxicity and reduce a number of experiments the development of predictive toxicity models is important. In this study, performed on a series of nanoparticles, the comparative Quantitative-Structure Activity Relationships (nano-QSARs) analyses of their toxicity towards E.coli and HaCaT cells were established. A new approach for representation of nanoparticles’ structure was presented. For description of supramolecular structure of nanoparticles “liquid drop” model was applied. It is expected that novel, proposed approach could be of general use for predictions related to nanomaterials. In addition, in our study fragmental simplex descriptors and several ligand-metal binding characteristics were calculated. The developed nano-QSAR models were validated and reliably predict toxicity of all studied metal oxide nanoparticles. Based on the comparative analysis of contributed properties in both models the LDM-based descriptors were revealed to have almost similar level of contribution to toxicity in both cases, while other parameters (van-der-Waals interactions, electronegativity and metal-ligand binding characteristics) have unequal contribution levels. In addition, the models developed here suggest different mechanisms of nanotoxicity for these two types of cells.
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Introduction

A group of metal oxide nanoparticles represents one of the most remarkable nanomaterials because of their outstanding magnetic, mechanical, catalytic, electronic, semiconducting and various other properties. Such properties depend greatly on nanoparticle’s size, structure, and shape and make them valuable components for broad range of applications, including industrial, medical, chemical, and scientific. Conservative market evaluated the production for metal oxide nanoparticles in 2012 at about 270,041 tons, likely rising to 1,663,168 tons by 2020.1

Most of the metal oxide nanoparticles are persistent and able to cause persistent stress to live organisms, including humans, when exposed to environment.2-4. Since metal oxides in nano-sizes exhibit peculiar physico-chemical properties that make them dramatically different from bulk-sized forms these nanomaterials were subjected extensively to various experimental studies, including environmental and toxicological.5,6

To reduce a number of experiments and reveal the mechanism of nano-sized metal oxides toxicity the combined experimental and computational modeling studies were performed by different research groups, resulting in development of various predictive models4,20. For example, the mathematical model based on quantum-chemically calculated descriptors to predict cytotoxicity of nano-sized metal oxides was recently reported6. In another study a QSAR model was built to predict cellular uptake for a series of nanoparticles separating the organic part (surface modifier) from the common core (metal and metal oxide core).7 Interesting study was performed by Zhang et al.8 where authors were able to find a correlation between band gap and cytotoxicity. They also performed oxidative stress assays tests for series of metal oxide nanoparticles.

For the last decade nanotoxicologists proposed several different mechanisms by which nanoparticles interact with cell systems and penetrate into microorganisms or cells.6,16,19,21-30. For example, some nanoparticles can penetrate into test-systems with no specific receptors on their outer surface. This uptake may be initiated by van-der-Waals forces, electrostatic charges and steric interactions (size, geometries, bonding).2 To describe this type of interactions various theoretical methods could be used, including quantum-chemical calculations (QC), empirical formulas and approaches/software commonly used to calculate theoretical descriptors, like ChemAxon,31 Dragon,32 CDK,33 and SiRMS (Simplex Representation of Molecular Structure) approach34.

Based on our experience with predictive QSAR modeling and especially with nanoparticles properties prediction6,8,10,11,34-43, we suggest that for successful description of properties or mechanisms it is beneficial to use a combination of descriptors which reflect nanoparticles’ structure for the different levels of organization: from single molecule to supramolecular ensemble of molecules.

Thus, to simplify the representation of possible interactions on the nano-level in the present work we have utilized a “liquid drop” model (LDM)44. This is a very first, innovative study that applies models developed in physics to describe interactions of nanomaterials with biological systems. The study opens a new way of inclusions of several vital characteristics of nanomaterials in general parameters that could be used to uncover complex phenomena of their effects on biomolecules. It is worth to note, that LDM is able to describe such important properties of nanoparticle as surface area, surface to volume ratio, etc. Also LDM-based descriptors are size-dependent, that allows applying them for the series of nanoparticles with same chemical composition, but different sizes. Therefore, we believe that the proposed approach could be of general use for predictions related to nanomaterials.

Besides of some specific interactions of nanoparticle’s surface with a target system several studies suggest that the mechanism of nanoparticles’ toxicity depends on release of ions from the surface6,16,17,45. Also Mathews46 proposed that ionic forms of metals are more active and explained this fact by the process of ion binding to biomolecules. In this connection Tatara47 attempted to obtain a QSAR model for toxicity of metal ions using several ion characteristics. In addition, Newman48 demonstrated that this approach was suitable for toxicity prediction of the same species. Based on this, in the current work we have applied similar ion characteristics to reflect the ability of metal ions to interact with membranes.

In summary, in the present study the new approaches were applied to perform a comparative analysis of the QSAR models based on metal oxide nanoparticles’ cytotoxicity to bacteria Escherichia coli (prokaryotic cells) and HaCaT cells (eukaryotic cells).

Materials and Methods

Biological activity data

The toxicity data for nano-sized metal oxides against E.coli and HaCaT cells were analyzed and all original experimental data were taken from our previous publications6,49. Datasets consist of 17 and 18 metal oxide nanoparticles well characterized and then tested against E.coli and HaCaT cells, respectively. Originally measured in vitro effective concentration EC₅₀ toxicity data (mol/L) were expressed as logarithm of the inverse molar concentration (log(1/EC₅₀)) response variables. The structures, investigated toxicity values and sizes of individual nanoparticles and aggregation sizes are given in Table 1.

Computational Details

The main idea of proposed here approach was to use a combination of simple descriptors which reflect nanoparticles’ structure for the different levels of organization: from single metal oxide molecule (i.e. chemical structure) to supramolecular ensemble of molecules (i.e. nanoparticle size). To characterize a single metal oxide structure at the 2D level a Simplex Representation of Molecular Structure (SiRMS)34 methodology was used. To simplify the representation of possible interactions at the nano-level without

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quantum-chemical modeling the “liquid drop” model (LDM) was utilized. In addition, the properties of single metal cations were expressed using Metal-ligand binding (MLB) theory. When applying these steps, extensive quantum-mechanical calculations for relatively large (from computational point of view) molecular clusters might be avoided.

**Simplex Representations of Molecular Structure**

The SiRMS (Simplex Representation of Molecular Structure) approach was used to encode the first level of organization of investigated objects. In the framework of SiRMS, any molecule (chemical structure) can be represented as a system of different simplexes (fragments of fixed composition and topology). This approach expands features of other methods of fragment representation, by providing ability to perform the differentiation of atoms in simplex not only by their type, but also based on the different characteristics of atoms (electronegativity, lipophilicity, van-der-Waals interactions, etc).

In the current study we utilized a 2D level of molecule’s representation to generate fragment simplified. Initially, a molecule was represented as a molecular graph. All vertices in graph that represent characteristic features of atom, for example type of atom, the connectivity of atoms in graph, and bond nature were considered. Then atoms in molecule were encoded on the basis of various physicochemical properties and subsequently the organization of values’ range into definite discrete groups was performed. In this study all values of atoms’ differentiation were clustered into groups corresponding to their electronegativity (A<1.5<B<2.0<C<2.5<D<3.5<F) and Lennard-Jones potential (A<0.01<B<0.02<C<0.4<D for depth of the potential well and A<2.5<B<3<C<3.5<D<4<F for distance at which potential reaches minimum). Example of differentiation is shown in Fig.1.

Since the electronegativity value of Al₂O₃ is equal to 1.61 and electronegativity of O is 3.5, after differentiation applied based on the above rule the initial molecule Al₂O₃ can be represented as B₂D₃.

After differentiation step molecular graphs were fragmentized to combination of simplexes. As a regular procedure, SiRMS approach utilize molecular fragment size of 2 to 4 atoms, however taking into account that the objects of study are metal oxides, the shorter molecular fragments (1 to 3 atoms) were considered. Example of fragmentation is shown in Fig.2.

As a result, the net number of fragments (simplexes) of each type was used as a descriptor in model development.

**Liquid Drop Model**

Innovative approach is proposed in our study. We have introduced a liquid drop model, LDM, in order to encode the nanoparticle clusters (aggregates) in a solution. In LDM, nanoparticle is represented as a spherical drop, where elementary particles (molecules) are densely packed and density of cluster is equal to mass density. In this model the minimum radius of interactions between elementary particles in cluster is described by Wigner-Seitz radius:

\[ r_W = \left( \frac{3M}{4\pi \rho N_A} \right)^{1/3} \]  

where \( M \) - molecular weight, \( \rho \) - mass density, \( N_A \) - Avogadro constant.

LDM assumes that the most probable nanoparticles’ shape is spherical (as well as shape of nanoparticles’ aggregates in water). Based on this assumption the method assumes that the number of molecules in nanocluster is equal to:

\[ n = \left( \frac{r_0}{r_W} \right)^3 \]  

where \( r_0 \) - nanoparticle’s radius.

The equation (2) shows that the smaller the particle, the higher the ratio of surface to volume is. In other words, decreasing size of a particle considerably increases its surface area. It distinguishes the nanoparticles’ surface molecules from the other molecules in volume. It means that interaction forces between molecules located inside of molecular volume are not compensated by interaction forces of the same molecules located on the surface, i.e. the molecules on the surface are in special circumstances (Fig. 3).
Based on that, the ratio of surface molecules ($F$) to molecules in volume is supposed to be significant:

$$F = 4n^{-1/2}$$ (3)

As a result, more specific and more interpretative descriptor ($SV$) is proposed that describes the ratio of surface molecules to molecules in volume:

$$(SV) = \frac{\text{surface molecules}}{\text{molecules in volume}} = \frac{F}{1-F}$$ (4)

Aggregation of nanoparticles also plays an important role in estimation of their toxicity\(^5\). For example, small nanoparticles can localize in organelles in contrary to larger ones. Aggregation parameter ($AP$) reflects ratio of particles in aggregate in comparing to size of single particle:

$$(AP) = \frac{\text{size of aggregate}}{\text{size of single particle}}$$ (5)

**Metal-Ligand Binding Characteristics**

Metal-ligand binding (MLB) theory pre-assumes that binding of metals to soft ligands on biomolecules plays an important role in toxicity exhibition\(^6\).

In the current study two ion characteristics (MLB) were used to describe ability of metal ion’s affinity to biochemical ligands: covalent index ($CI$) and cation polarizing power ($CPP$).

$$(CI) = \frac{\chi^2}{m}r$$ (6)

$$(CPP) = \frac{Z^2}{r}$$ (7)

**Model development. Random Forests method**

The relationships between measured toxicity and calculated descriptors were established with Random Forest (RF) regression method using the RandomForest package\(^52\).

RF is an ensemble classifier proposed by Breiman\(^53\). It constructs a series of decision trees which are used to classify a new sample. At the regression process the average of the individual tree predictions of all trees is combined to produce one final prediction. Every node in tree called “decision rule”. For example, a decision tree is shown in Fig. 4.

**Results and discussions**

**Model development**

At the initial preparatory step, a number of descriptors were generated. Then, non-significant, constant descriptors and descriptors with high cross-correlation ($r > 0.90$) were eliminated (one of two descriptors with cross-correlation). In RF approach the model fitting is performed by separate trees which are then combined to a final consensus model. Within each tree the highly correlated descriptors are avoided.

The initial datasets were split into training and test sets. Values of toxicity for both test-systems were clustered by their activity to three groups. The splitting of the dataset to training and test sets (for both HaCaT cells and E.coli sets) was the same for both cases and fulfill two conditions: 1) metal oxides from each activity group should be presented in both training and test sets; 2) metal oxides presented in test set should cover all types of oxides ($\text{MeO, Me}_2\text{O}_3, \text{MeO}_2$), similarly to training set. The splitting of data to training and test sets is displayed in Table 1.

\[ \text{Fig. 3} \text{ Liquid drop model of a nanoparticle. Interaction forces between molecules located in the volume (white circles); interaction forces of the molecules located on the surface on the nanoparticle (red circles).} \]

\[ \text{Fig. 4} \text{ An example of decision tree} \]
Then, QSAR tasks were processed using Random Forests regression (5 trees, 3 descriptors in each). The statistical fit of a QSAR model was assessed by correlation coefficient $R^2$ and root-mean-square error of prediction RMSE. The resultant models are characterized with adequate statistical parameters and do possess a good predicting ability. Table 2 summarizes statistical results for both endpoints.

<table>
<thead>
<tr>
<th>Metal oxide nanoparticle</th>
<th>$E_{coli}$ log(1/LC$_{50}$)</th>
<th>HaCaT cells log(1/LC$_{50}$)</th>
<th>Size, nm</th>
<th>Aggregation size, nm</th>
<th>Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al$_2$O$_3$</td>
<td>2.49</td>
<td>1.85</td>
<td>44</td>
<td>372</td>
<td>training</td>
</tr>
<tr>
<td>Bi$_2$O$_3$</td>
<td>2.82</td>
<td>2.5</td>
<td>90</td>
<td>2029</td>
<td>training</td>
</tr>
<tr>
<td>CoO</td>
<td>3.51</td>
<td>2.83</td>
<td>100</td>
<td>257</td>
<td>test</td>
</tr>
<tr>
<td>Cr$_2$O$_3$</td>
<td>2.51</td>
<td>2.3</td>
<td>60</td>
<td>617</td>
<td>training</td>
</tr>
<tr>
<td>Fe$_2$O$_3$</td>
<td>2.29</td>
<td>2.05</td>
<td>32</td>
<td>298</td>
<td>training</td>
</tr>
<tr>
<td>In$_2$O$_3$</td>
<td>2.87</td>
<td>2.87</td>
<td>30</td>
<td>224</td>
<td>training</td>
</tr>
<tr>
<td>La$_2$O$_3$</td>
<td>3.45</td>
<td>2.49</td>
<td>30</td>
<td>291</td>
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<tr>
<td>NiO</td>
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<td>2.31</td>
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<td>223</td>
<td>test</td>
</tr>
<tr>
<td>SiO$_2$</td>
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<td>2.12</td>
<td>150</td>
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<td>training</td>
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<tr>
<td>SnO$_2$</td>
<td>2.01</td>
<td>2.67</td>
<td>15</td>
<td>810</td>
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<tr>
<td>TiO$_2$</td>
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<td>1.76</td>
<td>46</td>
<td>265</td>
<td>training</td>
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<tr>
<td>V$_2$O$_5$</td>
<td>3.14</td>
<td>2.24</td>
<td>15</td>
<td>1307</td>
<td>training</td>
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<tr>
<td>WO$_3$</td>
<td>-</td>
<td>2.56</td>
<td>50</td>
<td>180</td>
<td>training</td>
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<tr>
<td>Y$_2$O$_3$</td>
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<td>2.21</td>
<td>38</td>
<td>1223</td>
<td>training</td>
</tr>
<tr>
<td>ZnO</td>
<td>3.45</td>
<td>3.32</td>
<td>71</td>
<td>189</td>
<td>training</td>
</tr>
<tr>
<td>ZrO$_2$</td>
<td>2.15</td>
<td>2.02</td>
<td>47</td>
<td>661</td>
<td>test</td>
</tr>
</tbody>
</table>

Specifications of developed models (predicted values, standard deviation data, plots of experimentally determined versus predicted values) are presented in Supplementary information.

**Model interpretation and comparative analysis**

As a result of RF modeling we obtained 6 significant descriptors for HaCaT keratinocytes and 7 descriptors for $E_{coli}$. Absolute impacts for each rule are presented in %. Descriptors $S_1$, $r_w$, $\rho$ are the same for both models.

List of important descriptors to HaCaT cell cytotoxicity:
- $S_1$ – unbonded two-atomic fragments $[Me] \ldots [Me]$, which were encoded based on SiRMS-derived descriptors, describing distance where potential reaches minimum at van-der-Waals interactions (43%);
- $r_w$ – Wigner-Seitz radius of oxide’s molecule (24%);
- $\rho$ – mass density (6 %);
- (CI) – covalent index of the metal ion (10%);

List of important descriptors to $E_{coli}$ cytotoxicity:
- $S_1$ – unbonded two-atomic fragments $[Me] \ldots [Me]$, which was encoded based on SiRMS-derived descriptors, encoding distance where potential reaches minimum at van-der-Waals interactions (7%);
- $S_2$ – SiRMS-derived electronegativity aligned [13] descriptor of oxides molecules – in a sense of the acid-base property of oxides. This parameter increases with a number of oxygens in molecule (3%);
- $S_3$ – tri-atomic fragments $[Me] - [O] - [Me]$, which were encoded by SiRMS-derived descriptors, encoding electronegativity (29%); (SV) – proportion of surface molecules to molecules in volume (7%).

To generalize classification of developed models all descriptors were combined into four groups: metal-ligand binding characteristics, LDM-based descriptors, SiRMS-based electronegativity’s descriptors and SiRMS-based van-der-Waals interactions’ descriptors.

The relative contributions of various descriptors (in %) based on decision rules are presented in Figure 5 (HaCaT cells) and Figure 6 ($E_{coli}$).

![Diagram of relative contribution (in %) of certain descriptors to toxicity (HaCaT cells)](image)

Let’s take a look at developed models closely. As it can be seen from Fig. 4 and Fig. 5, only contribution sizes of LDM-based descriptors (32% and 31%) are approximately equal in both cases. However, different contributions of other structural parameters in both cases suggest that nanoparticles show different mechanisms of toxicity towards HaCaT and $E_{coli}$.

It is important to note that the Wigner-Seitz radius for both models has close values: 24% for HaCaT cells and 22% for $E_{coli}$. Most probably, Wigner-Seitz radius can describe availability fraction of free molecules on the nanocluster’s surface, which actually could be responsible for cytotoxicity.
Both models involve a descriptor (ρ) that encodes a mass density, which is one of fundamental properties in LDM (6% for HaCaT cells and 2% for E.coli). In addition, the developed model for E.coli contains a descriptor (SV) which reflects a ratio of surface molecules to molecules in volume and has the contribution to the toxicity ca 7%. We assume that the difference between contributions of the mass density descriptors in both cells arises from varied interactions of nanoparticle surface with these cells. Also, we suppose, since HaCaT cells as eukaryotic cells (about 100nm) are much larger than E.coli bacteria cells (about 2nm), the interaction surface is larger for HaCaT cell and therefore the contribution of these kinds of descriptors is higher for eukaryotic cells.

Several studies suggest that the mechanism of metal oxide nanoparticles’ toxicity depends on release of ions from the surface45. Nanoparticles are characterized by a large surface area and it correlates with a high number of reactive surface molecules. Larger number of surface molecules contributes to massive oxidizing capabilities46. Earlier, it was suggested that nanoparticles can produce oxidative stress by generation of O$_2^\cdot$ and 'OH radicals, so-called reactive oxygen species (ROS):

\[
\begin{align*}
O_2 & \rightarrow O_2^\cdot \quad (8) \\
O_2^\cdot + H_2O_2 & \rightarrow 'OH + OH^- + O_2 \quad (9)
\end{align*}
\]

Nevertheless the straight link between ROS levels and the induction of toxic effects for different cell types is not explicitly proven yet, but most of the studies support that hypothesis.

In addition, size-dependent LDM-based descriptors may also indirectly describe another mechanism of toxicity. Since in some cases nanoparticles are smaller than cells or cellular organelles, it allows them to penetrate into these main biological systems, disrupting their normal function7,5.67. This mechanism links damage of organelles with size of nanoparticles.

According to values of LDM-based descriptors for E.coli case it is possible to assume that nanoparticles with larger values of Wigner-Seitz radius (smaller number of molecules present in general nanocluster’s volume) exhibit higher toxicity.

Van-der-Waals interactions (S$_1$) have a high impact in model of toxicity to HaCaT cells (43%). In contrast to this, contribution of van-der-Waals interactions to E.coli toxicity is considerably smaller (7%). This parameter is responsible for the number of contacts (interactions) between the molecules on surface and those that leave the surface and possibly interacts later with a cell. Therefore, this can contribute to transport of molecule (or cation) to the media or periplasmatic space in the cells. Since eukaryotic cells are capable of internationalizing MOx nanoparticles much easier, the process of detachment from the surface may occur inside the cell. This mechanism is in agreement with the second mechanism of toxicity cased by nano metal oxides explained in our recent study79.

The difference in contributions of vDW descriptor also could be explained by considerably large difference in cell sizes for both considered cell systems. It seems that larger number of unbounded metal oxide molecules interact per cell in case of eukaryotic cells, i.e. HaCaT cells.

Descriptors S$_2$ are different in both models, but have high correlation. It means that there is a possibility to compare impacts of these descriptors. In case of HaCaT cells the value of this descriptor has relatively high impact (15%), comparing with E.coli (3%). As these descriptors are related to a number of oxygen’s atoms in a molecule, the smaller electronegativity impact is linked to higher toxicity. This parameter characterizes acid-base properties of oxides and increases with a number of oxygens in a molecule. Descriptor S$_3$ also represents the electronegativity in case of E.coli toxicity and has high impact (29%). Thus, the contribution of whole electronegativity is about twice as large for E.coli (32%), comparing with HaCaT cells (15%).

Descriptors of MLB characteristics for the HaCaT cells and E.coli toxicity are different. Covalent index (10%) in a model of toxicity to HaCaT cells reflects the interaction with protein-bound sulphydryl’s and depleting of glutathione75. Cation polarization power (30%) in a model of toxicity to E.coli reflects electrostatic interactions75 and also this comes in agreement with the prevailing impact of SiRMS descriptors, which reflects electronegativity.

The overall schematic representation of suggested mechanisms are showed in Figure 7 (for HaCaT cell) and in Figure 8 (for E.coli cell).

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**Fig. 6** Diagram of relative contribution (in %) of certain descriptors to toxicity (E.coli cells)

**Fig. 7** Schematic representation of the mechanism of metal oxide nanoparticle toxicity for HaCaT cell

**Fig. 8** Schematic representation of the mechanism of metal oxide nanoparticle toxicity for E.coli cell

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**Conclusions**

In the present study we combined the analysis of two different experimental toxicity data of metal oxide nanoparticles to E.coli cells and HaCaT cells. We have utilized a computational modeling methodology to build classification models for quick predictions and to find the difference in contributions of various properties to
each type of toxicity (E.coli or HaCaT). The developed nano-QSAR models were validated and reliably predict toxicity for all studied metal oxide nanoparticles. Based on the comparative analysis of properties’ contribution in both nano-QSAR models we have found that LDM-based descriptors have almost similar level of contributions to toxicity in both cases, while other parameters (van-der-Waals interactions, electronegativity and metal-ligand binding characteristics) have different contribution levels. Thus, the developed nano-QSAR models reveal the differences in the mechanisms of toxicity of metal oxide nanoparticles to bacteria and a human keratinocyte cell line, which belong to prokaryotic and eukaryotic systems, respectively.

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