Assessment of Cytotoxicity of Metal Oxide Nanoparticles on the Basis of Fundamental Physical-Chemical Parameters: a Robust Approach to Grouping

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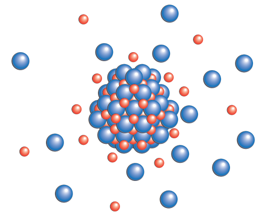
OBJECTIVE: RAPID, TRANSPARENT, AND ACCESSIBLE ASSESSMENT OF THE CYTOTOXICITY OF NANOPARTICLES

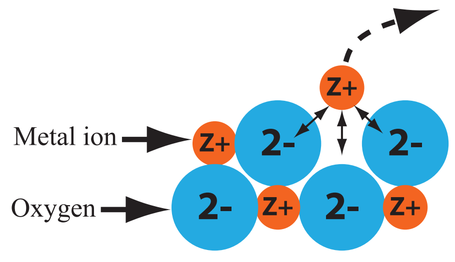
1. Properties of Nanoparticles known for contributing to hazard

2. Physical-chemical interpretation

3. Fundamental Physical-Chemical parameters determining the hazardous mechanisms in 1.



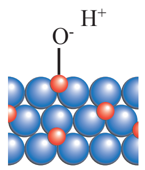
Release of Ions



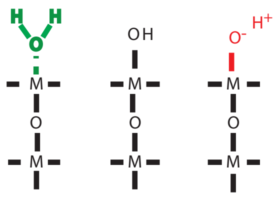
The strenght of the electrostatic forces in the lattice determines the rate of the release of ions from a nanoparticle into an aqueous environment. NP that release ions tend to be more toxic than stable, inert NP.

Z. Oxidation Number.

It is the formal charge of the metal ion, which determines the strenght of the electrostatic forces. Z can be calculated from the chemical formula, recalling that, in an oxide, oxygen has always Z=-2. The higher the value of Z, the lower the rate of ion release.



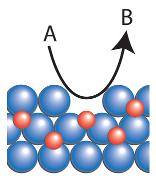
Surface Charge



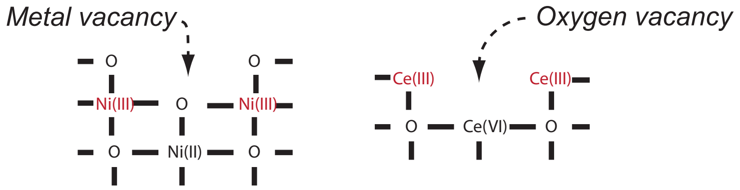
Surface charge mainly due to the degree of hydrolysis, which is determined by the intensity of the electric field generated by a cation. Positively charged surfaces tend to be more toxic than negatively charged ones.

IP=Z/r. Ionic Potential.

It is defined as the ratio of the formal charge (Z) to the ionic radius (r), and measures the intensity of the electric field generated by an ion. The ionic radii of all elements have been determined and can be easily found. The higher the IP, the more negatively charged is the oxide (i.e.,more acid).



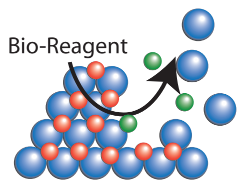
Surface Reactivity



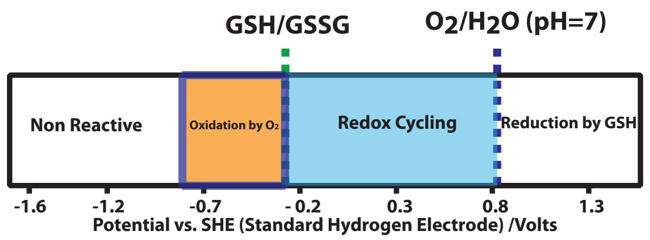
The nature of defects at the surface contribute to the surface reactivity. The redox states allowed for the metal ion determine the nature of the defect. Reducible ions (e.g., Ce) tend to form oxygen vacancies, while oxidizble ions (e.g., Ni) tend to form metal vacancies.

Reducibility.

The reducibility of an oxide depends on the allowed oxidation states of the metal ion. These oxidation states are often listed in a periodic table. Oxidizable oxides (e.g., NiO) tend to be more cytotoxic than reducible ones (e.g., CeO_2)



Bulk Reactivity



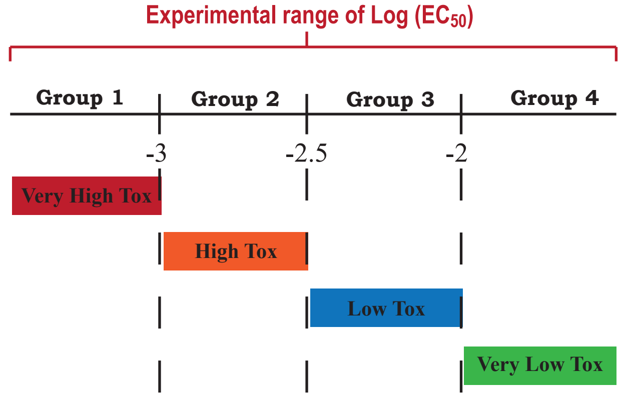
A nanoparticle can interfere (i.e., react) with the redox window of a cell, defined, on the negative side, by the redox potential of Glutathione (GSH), and, on the positive side, by the redox potential of dissolved oxygen. Reactive NP tend to be more toxic than Non reactive.

Redox Potential.

Depending on the value of the redox potential of the oxide, a nanoparticle can be chemically REACTIVE or NON REACTIVE. The value of the redox potential can be calculated with the Nernst Equation. Values of Standard Redox Potential can be easily found.

Grouping Strategy:

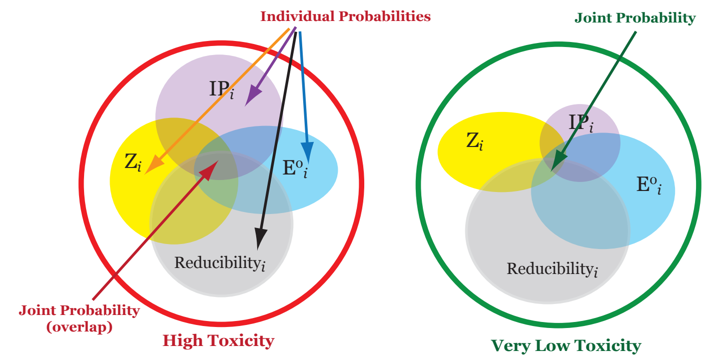
classification of nanoparticles according to their cytotoxicity as quantified by the value of EC_{50}, the concentration (mol/L) that reduces cells' availability by 50%. The reported experimental values of EC_{50} suggested four groups defined as ranges of values of EC_{50}:



Probabilistic Grouping

Given a nanoparticle NP_i with oxidation number of the cation Z_i, Ionic Potential of the cation IP_i, $Reducibility_i$ (i.e., Reducible, or Oxidizable), and redox potential at pH=7 $E^0{}_i$

the probability that NP_i belongs to one of the groups of toxicity defined above is given by the joint probability of the probabilities of specific values of the physical chemical parameters whithin that toxicity group. (e.g., *how many times the value Z_i appears in the Hight Toxicity group? And so on for all values of all the other parameters*)



Given the chemical formula of an oxide nanoparticle, the individual probabilities can be estimated from historical outcomes. Notably, the values of the fundamental physical-chemical parameters **Z, IP, Reducibility, and Redox Potential** **do not ned any experimental quanification:** grouping can be achieved with the help of just a **periodic table** and a **pocket calculator.**

Details in: https://doi.org/10.1039/C9EN00785G