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

   Release of Ions
   - Metal ion: 2-
   - Oxygen: 2-
   - Oxidation number (Z): 2-
   - Reduced ion: Z-
   - Oxidation by O2
   - Redox Cycling
   - Oxidation potential: Z/r
   - Ionic Potential (IP) = Z/r
   - Surface Charge
   - Bulk Reactivity
   - Bio-Reagent

2. Physical-chemical interpretation

   Z. Oxidation Number.
   - It is the formal charge of the metal ion, which determines the strength 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.

   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 higher the IP, the more negatively charged surfaces tend to be more toxic than negatively charged ones.

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

   - 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 oxides (e.g., CeO₂).

   - 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 EC₅₀, the concentration (mol/L) that reduces cells' availability by 50%.
- The reported experimental values of EC₅₀ suggested four groups defined as ranges of values of EC₅₀:

<table>
<thead>
<tr>
<th>Group</th>
<th>Log(EC₅₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; -3</td>
</tr>
<tr>
<td>2</td>
<td>-3 to -2.5</td>
</tr>
<tr>
<td>3</td>
<td>-2.5 to -2</td>
</tr>
<tr>
<td>4</td>
<td>&gt; -2</td>
</tr>
</tbody>
</table>

- High Toxicity
- Medium Toxicity
- Low Toxicity
- Very Low Toxicity

Probabilistic Grouping
- Given a nanoparticle NP, with oxidation number of the cation Z₄, Ionic Potential of the cation IP, Reducibility (i.e., Reducible, or Oxidizable), and redox potential at pH=7 E₀,
- the probability that NP 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 within that toxicity group.
- And so on for all values of all the other parameters.

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