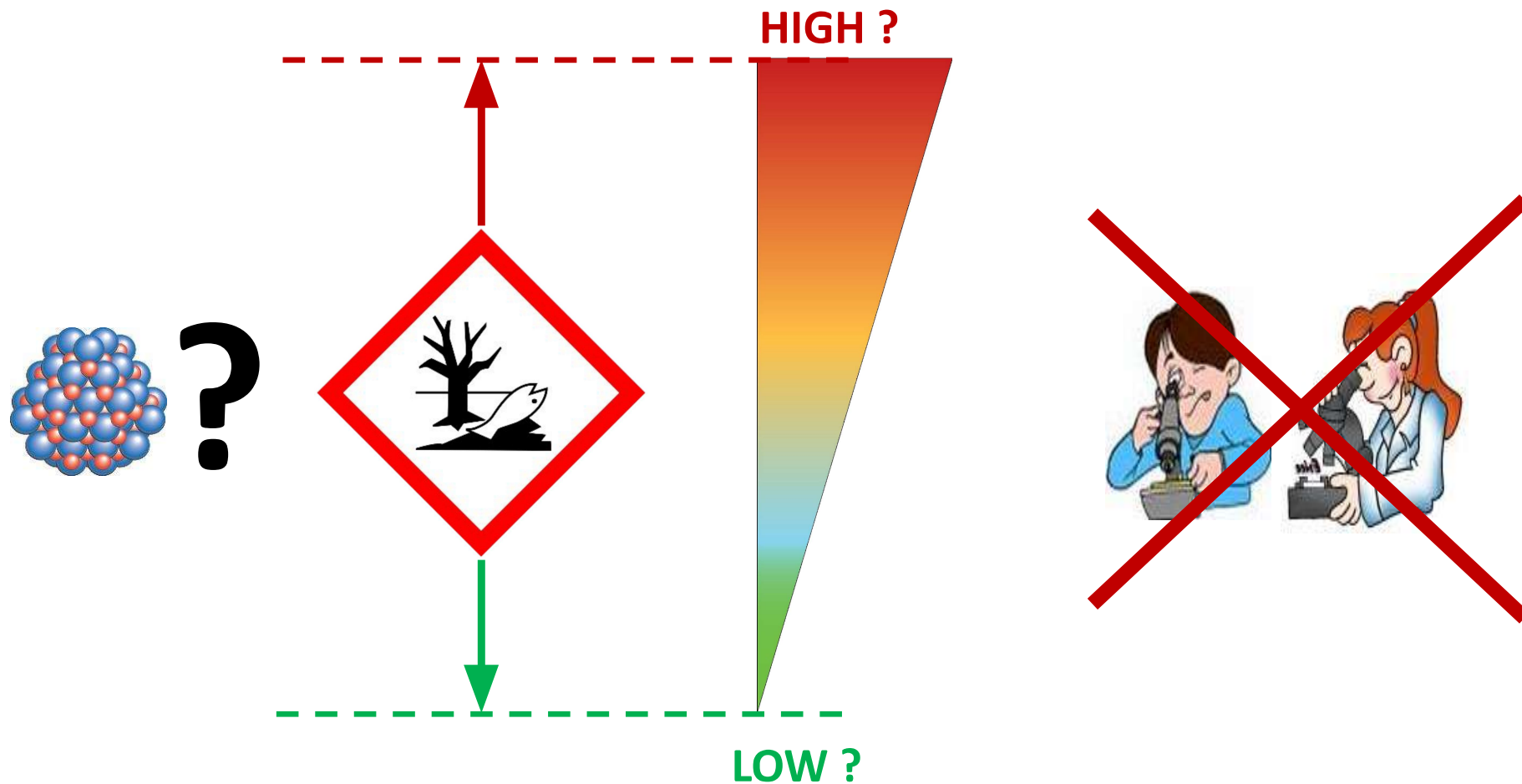
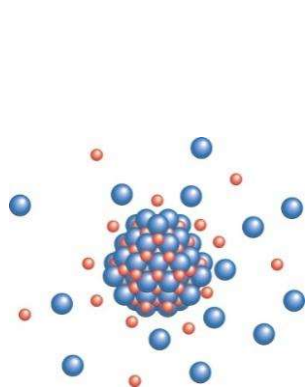


**Assessment of Cytotoxicity of Metal Oxide Nanoparticles
on the Basis of **Immediately Available**
Physical-Chemical Parameters**

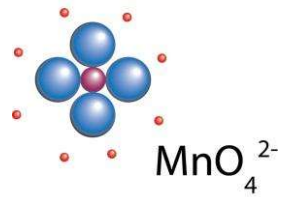
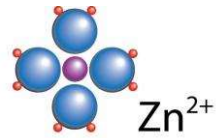
CNR-ISTEC -ITALY
felice.simeone@istec.cnr.it

Hazard of a Nanoparticle **Before** Running any Experiment

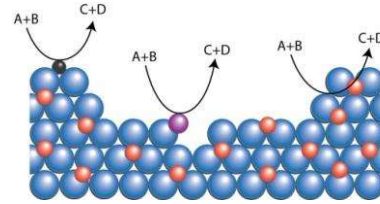




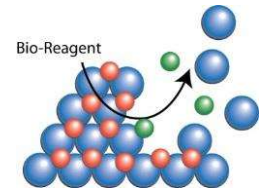
Dissolution



Surface charge



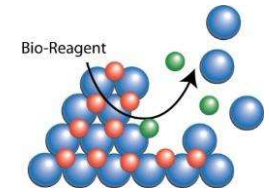
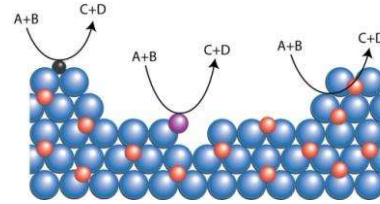
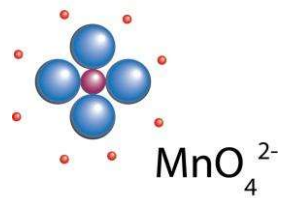
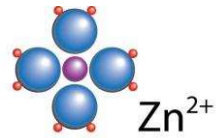
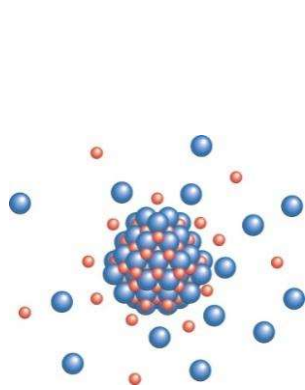
Surface reactivity



Bulk reactivity



Hazard



Dissolution

Surface charge

Surface reactivity

Bulk reactivity

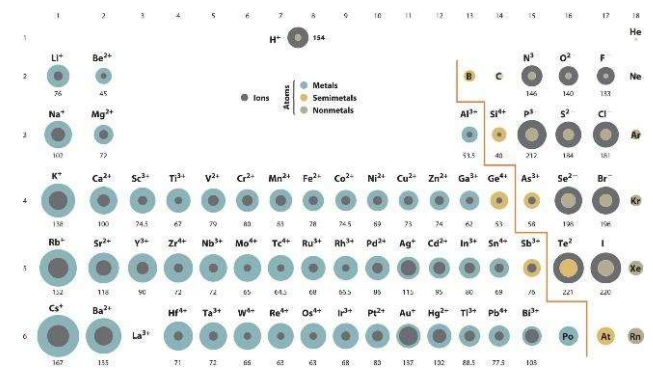
Z

Z/r

Reducibility

Redox Potential

Hazard



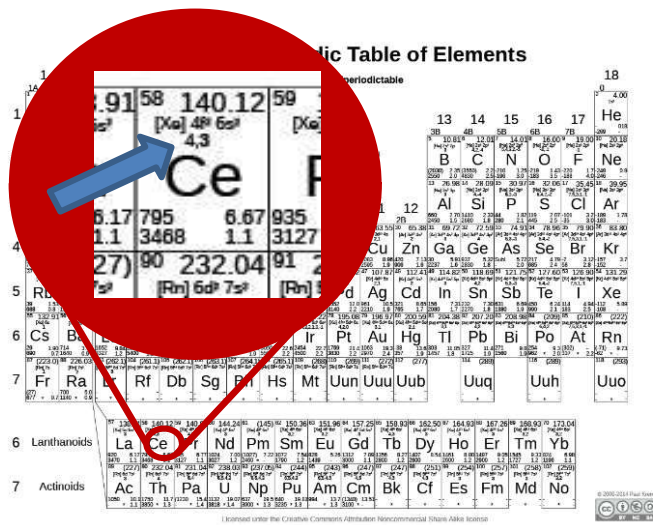
Z
Oxidation number
given by the Chemical Formula

Ionic Potential = Z/r
Ionic Radii Measured in the '30
(Available on the Internet)

Hazard

Reducibility deduced
from a Periodic Table

Redox Potential
available everywhere



Reaction	Log K at 25°C	Standard Electrode Potential (V) at 25°C
$\text{Na}^+ + \text{e}^- = \text{Na(s)}$	-46	-2.71
$\text{Mg}^{2+} + 2\text{e}^- = \text{Mg(s)}$	-79.7	-2.35
$\text{Zn}^{2+} + 2\text{e}^- = \text{Zn(s)}$	-26	-0.76
$\text{Fe}^{2+} + 2\text{e}^- = \text{Fe(s)}$	-14.9	-0.44
$\text{Co}^{2+} + 2\text{e}^- = \text{Co(s)}$	-9.5	-0.28
$\text{V}^{3+} + \text{e}^- = \text{V}^{2+}$	-4.3	-0.26
$2\text{H}^+ + 2\text{e}^- = \text{H}_2(\text{g})$	0.0	0.00
$\text{S(s)} + 2\text{H}^+ + 2\text{e}^- = \text{H}_2\text{S}$	+4.8	+0.14
$\text{Cu}^{2+} + \text{e}^- = \text{Cu}^+$	+2.7	+0.16
$\text{AgCl(s)} + \text{e}^- = \text{Ag(s)} + \text{Cl}^-$	+3.7	+0.22
$\text{Cu}^{2+} + 2\text{e}^- = \text{Cu(s)}$	+11.4	+0.34
$\text{Cu}^+ + \text{e}^- = \text{Cu(s)}$	+8.8	+0.52
$\text{Fe}^{3+} + \text{e}^- = \text{Fe}^{2+}$	+13.0	+0.77
$\text{Ag}^+ + \text{e}^- = \text{Ag(s)}$	+13.5	+0.80
$\text{Fe(OH)}_3(\text{s}) + 3\text{H}^+ + \text{e}^- = \text{Fe}^{2+} + 3\text{H}_2\text{O}$	+17.1	+1.01
$\text{IO}_3^- + 6\text{H}^+ + 5\text{e}^- = \frac{1}{2}\text{I}_2(\text{s}) + 3\text{H}_2\text{O}$	+104	+1.23
$\text{MnO}_2(\text{s}) + 4\text{H}^+ + 2\text{e}^- = \text{Mn}^{2+} + 2\text{H}_2\text{O}$	+43.6	+1.29
$\text{Cl}_2(\text{g}) + 2\text{e}^- = 2\text{Cl}^-$	+46	+1.36
$\text{Co}^{3+} + \text{e}^- = \text{Co}^{2+}$	+31	+1.82



Risk Assessment

Periodic Table of the Elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
H	He											B	C	N	O	F	Ne
Li	Be									Na	Mg	Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac	Rf	Ha	Hg	Nh	Fl	Mc	Lv	Tl	Uu	Cu	Uu	Uu	Uu	Uu	Uu

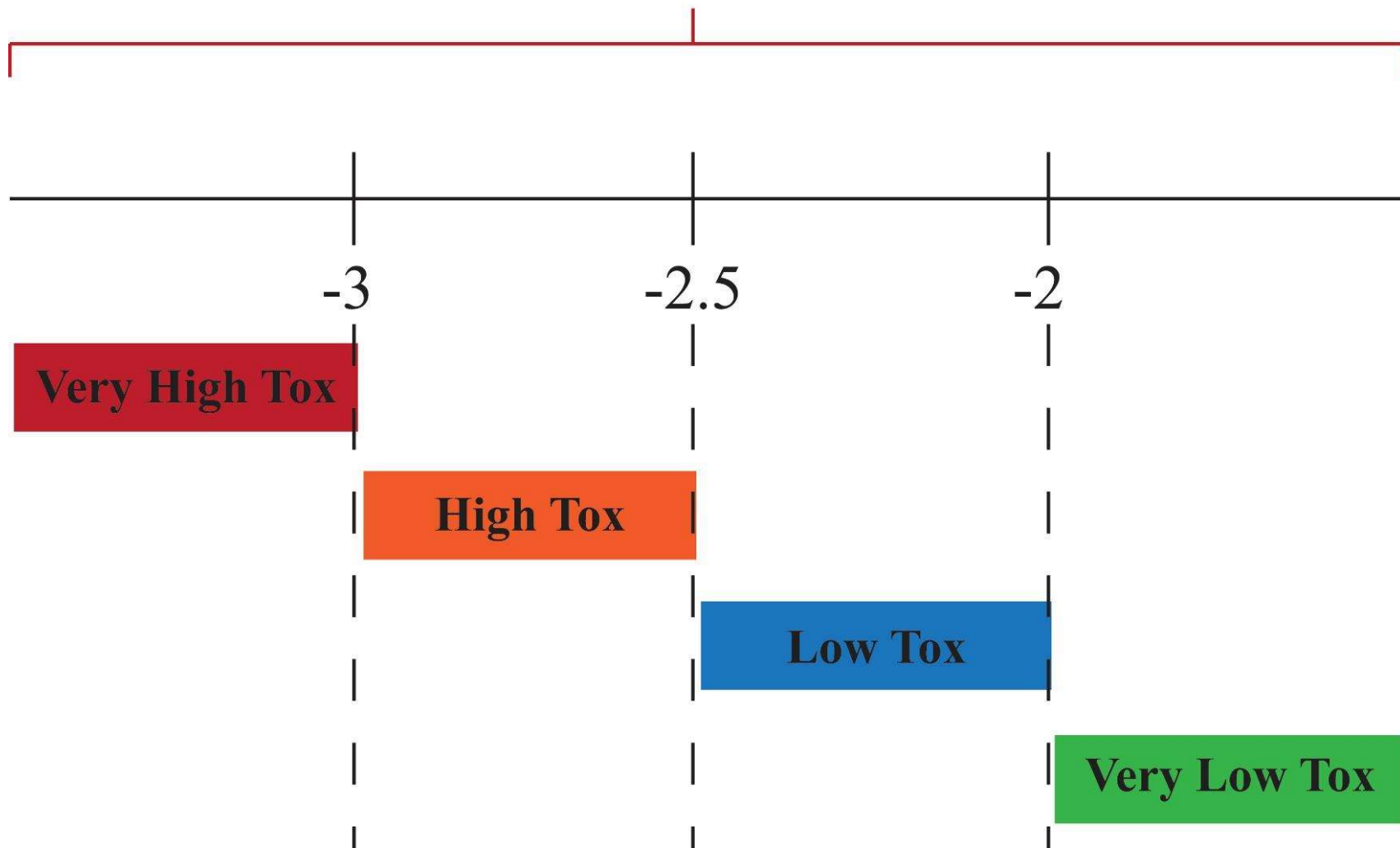
* Lanthanide Series
58 Ce 59 Pr 60 Nd 61 Pm 62 Sm 63 Eu 64 Gd 65 Tb 66 Dy 67 Ho 68 Er 69 Tm 70 Yb 71 Lu

* Actinide Series
90 Th 91 Pa 92 U 93 Np 94 Pu 95 Am 96 Cm 97 Bk 98 Cf 99 Es 100 Fm 101 Md 102 No 103 Lr



Definition of classes of toxicity

Experimental range of Log (EC₅₀)

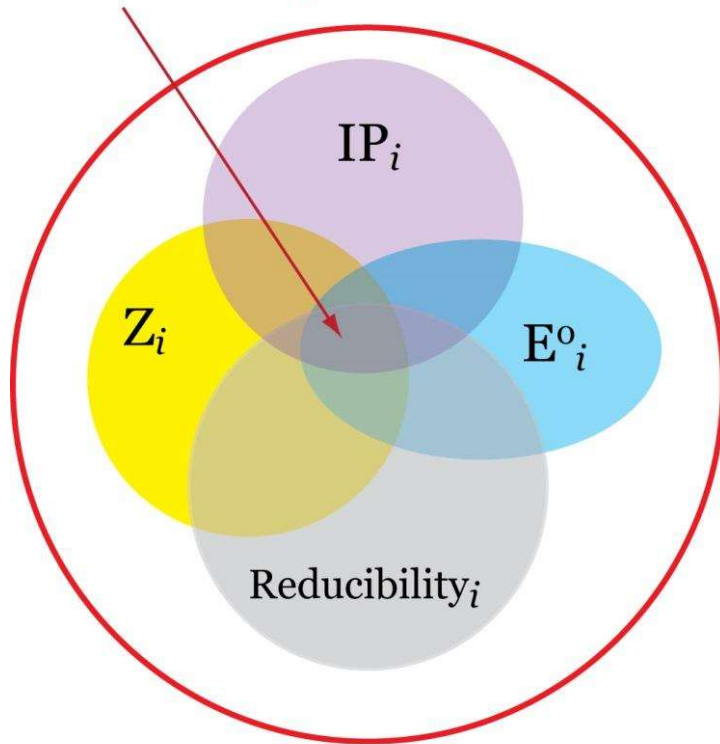


Oxide	Oxidation		Ionic		Surface		Redox		Class of Toxicity (Experimental)
	Number	Z	Potential	IP	Reducibility	SR	Reactivity	RR	
ZnO	≤ 2		≤ 3		Non Reducible		Non Active		Very high toxicity
NiO	≤ 2		≤ 3		Oxidizable		Active		Very high toxicity
Mn ₂ O ₃	3		> 5		Oxidizable		Active		Very high toxicity
Cr ₂ O ₃	3		3-5		Oxidizable		Active		High toxicity
Y ₂ O ₃	3		3-5		Reducible		Non Active		High toxicity
Bi ₂ O ₃	3		≤ 3		Oxidizable		Active		High toxicity
MoO ₃	> 4		> 5		Reducible		Active		High toxicity
Gd ₂ O ₃	3		≤ 3		Reducible		Non Active		High toxicity
V ₂ O ₃	3		3-5		Oxidizable		Active		High toxicity
ZrO ₂	≥ 4		> 5		Reducible		Non Active		Low toxicity
Al ₂ O ₃	3		> 5		Reducible		Non Active		Low toxicity
TiO ₂	≥ 4		> 5		Reducible		Non Active		Very low toxicity
SiO ₂	≥ 4		> 5		Non reducible		Non Active		Very low toxicity
HfO ₂	≥ 4		> 5		Reducible		Non Active		Very low toxicity
WO ₃	≥ 4		> 5		reducible		Non Active		Very low toxicity

Naive Bayes Classifier

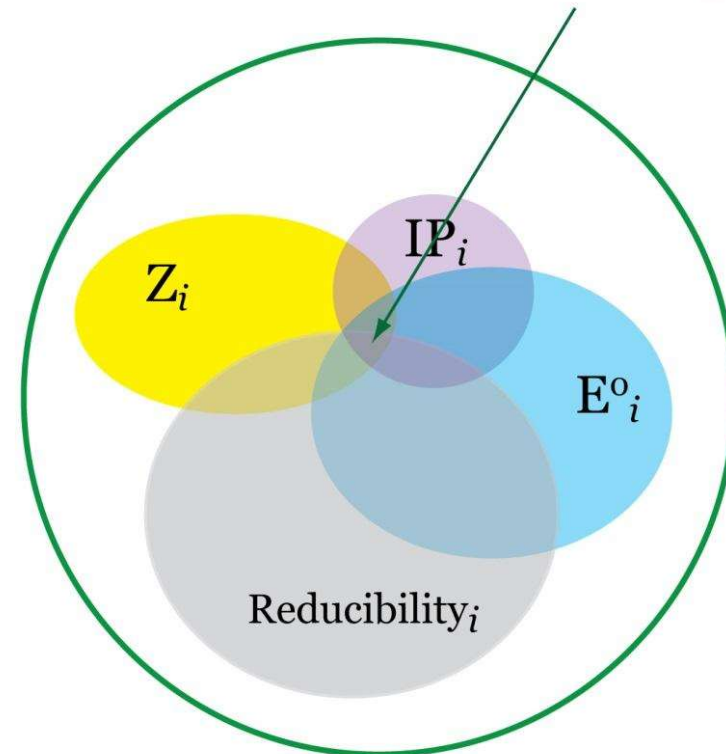
Most probable level of toxicity of $NP_i = [Z_i, IP_i, SR_i, RR_i]?$

Joint Probability



High Toxicity

Joint Probability



Very Low Toxicity

$$P(\text{Tox}|NP_i) \propto P(Z_i|\text{Tox}) \times P(IP_i|\text{Tox}) \times P(SR_i|\text{Tox}) \times P(RR_i|\text{Tox})$$

ZnO

 $Z \leq 2$ $IP \leq 3$

Non Reducible

Non Active


Z	IP	SR	RR
Oxidation Number	Ionic Potential	Surface Reducibility	Redox Reactivity
$P(Z \leq 2 VT) = 0.666$	$P(IP \leq 3 VT) = 0.666$	$P(SR = NR VT) = 0.333$	$P(RR = A^d VT) = 0.665$
$P(Z \leq 2 HT) = 0.001^*$	$P(IP \leq 3 HT) = 0.333$	$P(SR = NR HT) = 0.001^*$	$P(RR = A HT) = 0.665$
$P(Z \leq 2 LT) = 0.001^*$	$P(IP \leq 3 LT) = 0.001^*$	$P(SR = NR LT) = 0.001^*$	$P(RR = A LT) = 0.001^*$
$P(Z \leq 2 VL) = 0.001^*$	$P(IP \leq 3 VL) = 0.001^*$	$P(SR = NR VL) = 0.249$	$P(RR = A VL) = 0.001^*$
$P(Z = 3 VT) = 0.333$	$P(IP = 3-5 VT) = 0.001^*$	$P(SR = R^b VT) = 0.001^*$	$P(RR = NA VT) = 0.335$
$P(Z = 3 HT) = 0.833$	$P(IP = 3-5 HT) = 0.501$	$P(SR = R HT) = 0.500$	$P(RR = NA HT) = 0.335$
$P(Z = 3 LT) = 0.500$	$P(IP = 3-5 LT) = 0.001^*$	$P(SR = R LT) = 0.998$	$P(RR = NA LT) = 0.999$
$P(Z = 3 VL) = 0.001^*$	$P(IP = 3-5 VL) = 0.001^*$	$P(SR = R VL) = 0.750$	$P(RR = NA VL) = 0.999$
$P(Z \geq 4 VT) = 0.001^*$	$P(IP > 5 VT) = 0.333$	$P(SR = O^c VT) = 0.666$	
$P(Z \geq 4 HT) = 0.166$	$P(IP > 5 HT) = 0.166$	$P(SR = O HT) = 0.499$	
$P(Z \geq 4 LT) = 0.499$	$P(IP > 5 LT) = 0.998$	$P(SR = O LT) = 0.001^*$	
$P(Z \geq 4 VL) = 0.998$	$P(IP > 5 VL) = 0.998$	$P(SR = O VL) = 0.001^*$	

$$P(\text{ZnO} | VT) = 0.666 \times 0.666 \times 0.333 \times 0.335 = \mathbf{0.05}$$

$$P(\text{ZnO} | HT) = 0.001 \times 0.333 \times 0.001 \times 0.335 = \mathbf{0.0000005}$$

$$P(\text{ZnO} | LT) = 0.001 \times 0.001 \times 0.001 \times 0.999 = \mathbf{0.000000001}$$

$$P(\text{ZnO} | VL) = 0.001 \times 0.001 \times 0.249 \times 0.299 = \mathbf{0.00000007}$$



MODEL
Title: Naive Bayes model for the prediction of cytotoxicity of metal oxide nanoparticles
Owner: Haralambos Sarimveis
Description:
Naive Bayes model for the prediction of cytotoxicity of metal oxide nanoparticles using fundamental physical-chemical parameters

Choose method

Predict

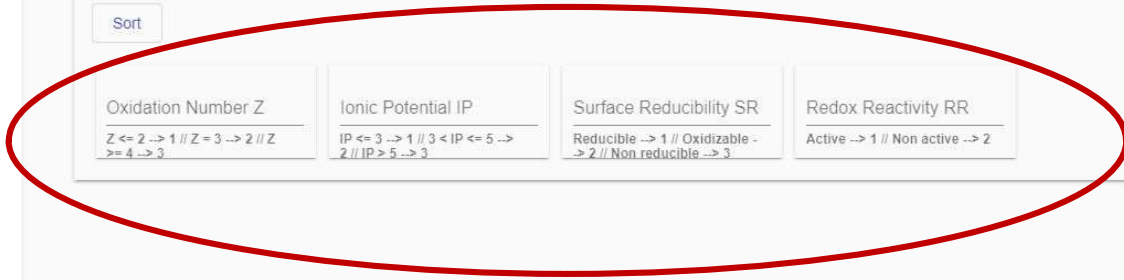
Upload dataset with the required independent features and values

↓ ↑

Input values for the independent features

Sort

Oxidation Number Z Z <= 2 -> 1 // Z = 3 -> 2 // Z >= 4 -> 3	Ionic Potential IP IP <= 3 -> 1 // 3 < IP <= 5 -> 2 // IP > 5 -> 3	Surface Reducibility SR Reducible -> 1 // Oxidizable -> 2 // Non reducible -> 3	Redox Reactivity RR Active -> 1 // Non active -> 2
---	--	---	--



Fill in values, using appropriate encoding values

When ready hit the start button

Download results

Upload dataset with the required independent features and values

↓ ↑

Input values for the independent features

Sort

Oxidation Number Z 2 Z <= 2 -> 1 // Z = 3 -> 2 // Z >= 4 -> 3	Ionic Potential IP 1 IP <= 3 -> 1 // 3 < IP <= 5 -> 2 // IP > 5 -> 3	Surface Reducibility SR 2 Reducible -> 1 // Oxidizable -> 2 // Non reducible -> 3	Redox Reactivity RR 2 Active -> 1 // Non active -> 2
---	--	---	--

Start

View predicted value only

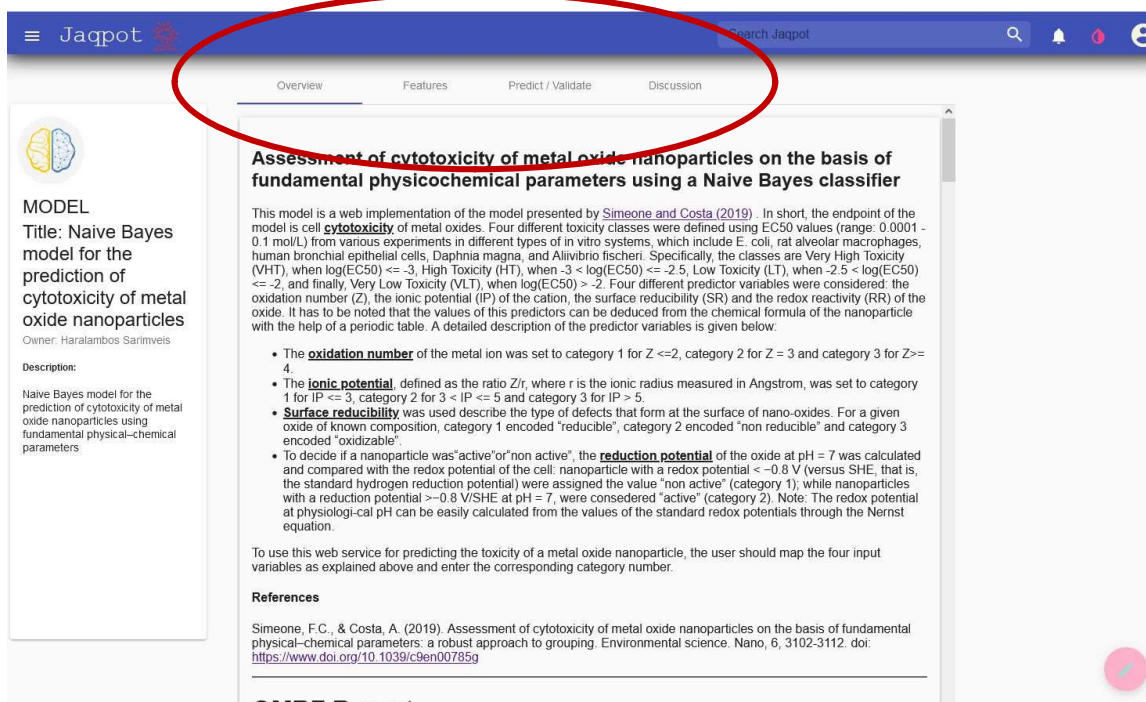
Id	Redox Reactivity RR	Class of toxicity	Oxidation Number Z	Surface Reducibility SR	Ionic Potential IP
0	2	VHT	2	2	1

Items per page: 30 1 - 1 of 1 < >

Download

Model Page Tabs

- ‘**Overview**’ contains information on the model;
- ‘**Features**’ documents the encoding and units of the features;
- ‘**Predict/Validate**’ allows prediction and validation of the model;
- ‘**Discussion**’ allows end-users to leave comments, thoughts and ideas on the model;



The screenshot displays the Jaqpot web interface. At the top, there is a navigation bar with the Jaqpot logo and a search bar. Below the navigation bar, there are four tabs: Overview, Features, Predict / Validate, and Discussion. A red circle highlights these tabs. The main content area shows the title of a model: "Assessment of cytotoxicity of metal oxide nanoparticles on the basis of fundamental physicochemical parameters using a Naive Bayes classifier". The description of the model is provided, along with a list of features and their encodings. The features listed are: oxidation number, ionic potential, and surface reducibility. The description also includes a reference to Simeone and Costa (2019).

MODEL
Title: Naive Bayes model for the prediction of cytotoxicity of metal oxide nanoparticles
Owner: Haralambos Sarimveis

Description:
Naive Bayes model for the prediction of cytotoxicity of metal oxide nanoparticles using fundamental physical-chemical parameters

Assessment of cytotoxicity of metal oxide nanoparticles on the basis of fundamental physicochemical parameters using a Naive Bayes classifier

This model is a web implementation of the model presented by Simeone and Costa (2019). In short, the endpoint of the model is cell **cytotoxicity** of metal oxides. Four different toxicity classes were defined using EC50 values (range: 0.0001 - 0.1 mol/L) from various experiments in different types of in vitro systems, which include E. coli, rat alveolar macrophages, human bronchial epithelial cells, Daphnia magna, and Alivibrio fischeri. Specifically, the classes are Very High Toxicity (VHT), when $\log(\text{EC50}) \leq -3$, High Toxicity (HT), when $-3 < \log(\text{EC50}) \leq -2.5$, Low Toxicity (LT), when $-2.5 < \log(\text{EC50}) \leq -2$, and finally, Very Low Toxicity (VLT), when $\log(\text{EC50}) > -2$. Four different predictor variables were considered: the oxidation number (Z), the ionic potential (IP) of the cation, the surface reducibility (SR) and the redox reactivity (RR) of the oxide. It has to be noted that the values of this predictors can be deduced from the chemical formula of the nanoparticle with the help of a periodic table. A detailed description of the predictor variables is given below.

- The **oxidation number** of the metal ion was set to category 1 for $Z \leq -2$, category 2 for $Z = 3$ and category 3 for $Z \geq 4$.
- The **ionic potential**, defined as the ratio Z/r , where r is the ionic radius measured in Angstrom, was set to category 1 for $\text{IP} \leq 3$, category 2 for $3 < \text{IP} \leq 5$ and category 3 for $\text{IP} > 5$.
- **Surface reducibility** was used to describe the type of defects that form at the surface of nano-oxides. For a given oxide of known composition, category 1 encoded "reducible", category 2 encoded "non reducible" and category 3 encoded "oxidizable".
- To decide if a nanoparticle was "active" or "non active", the **reduction potential** of the oxide at $\text{pH} = 7$ was calculated and compared with the redox potential of the cell: nanoparticle with a redox potential < -0.8 V (versus SHE, that is, the standard hydrogen reduction potential) were assigned the value "non active" (category 1); while nanoparticles with a reduction potential > -0.8 V/SHE at $\text{pH} = 7$, were considered "active" (category 2). Note: The redox potential at physiological pH can be easily calculated from the values of the standard redox potentials through the Nernst equation.

To use this web service for predicting the toxicity of a metal oxide nanoparticle, the user should map the four input variables as explained above and enter the corresponding category number.

References

Simeone, F.C., & Costa, A. (2019). Assessment of cytotoxicity of metal oxide nanoparticles on the basis of fundamental physical-chemical parameters: a robust approach to grouping. Environmental science. Nano, 6, 3102-3112. doi: <https://www.doi.org/10.1039/c9en00785g>



Risk Assessment

Periodic Table of the Elements

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
H	He	Li	Be	B	C	N	O	F	Ne	Na	Mg	Al	Si	P	S	Cl	Ar	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn	Fr	Ra	Ac	Rf	Ha	Hs	Mt	110	111	112	113	114	115	116	117	118	119	120																														
		* Lanthanide Series										* Actinide Series																																																																																																											
		Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr																																																																																										



Felice C. Simeone
National Research Council of Italy
(*Consiglio Nazionale delle Ricerche*)

felice.simeone@istec.cnr.it

Acknowledgments

Harry Sarimveis

Anna L. Costa