Towards Understanding Mechanisms Governing Cytotoxicity of Metal Oxides Nanoparticles: Hints from Nano-QSAR Studies

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Supplementary material

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Symbols and definitions of all calculated molecular descriptors

TABLE S1

Symbol	Definition of molecular descriptor	Included in the model?
QUANTUM - MECHANICAL DESCRIPTORS		
ΔH_f^c	Standard enthalpy of formation of metal oxide nanocluster	Yes
TE	Total energy	No
EE	Electronic energy	No
Core	Core–core repulsion energy	No
SAS	Solvent accessible surface	No
HOMO	Energy of the Highest Occupied Molecular Orbital	No
LUMO	Energy of the Lowest Unoccupied Molecular Orbital	No
η	Chemical hardness	No
S	Total softness	No
E_g	HOMO-LUMO energy gap	No
μ	Electronic chemical potential	No
E_v	Valance band	No
E_c	Conduction band	No
χ^c	Mulliken's electronegativity	Yes
Hard	Parr and Pople's absolute hardness	No
Shift	Schuurmann MO shift alpha	No
Ahof	Polarizability derived from the heat of formation	No
Ad	Polarizability derived from the dipole moment	No
IMAGE DESCRIPTORS		
A	Area	No
V	Volume	No
d_s	Surface diameter	No
$d_{v/m}$	Volume/mass diameter	No
d_{Sauter}	Volume/surface diameter	No
A_{R_x}	Aspect ratio X	No
A_{R_y}	Aspect ratio Y	No
P_x	Porosity X	No
P_y	Porosity Y	No
Ψ	Sphericity	No
f_{circ}	Circularity	No

Crystallographic data utilized to construct the metal oxides clusters

TABLE S2

Metal oxide	Reference
Al ₂ O ₃	Kondo, S., Tateishi K., Ishizawa N., <i>Structural Evolution of Corundum at High Temperatures</i> . Japanese Journal of Applied Physics, 2008. 47 : p. 616-619
Bi ₂ O ₃	Cornei, N., Tancret N., Abraham F., Mentré O., New epsilon-Bi ₂ O ₃ metastable polymorph. Inorganic Chemistry, 2006. 26 : p. 4886-4888.
CoO	Saito, S., Nakahigashi K., Shimomura Y., X-Ray Diffraction Study on CoO. Journal of the Physical Society of Japan, 1966. 21 : p. 850-860.
Cr ₂ O ₃	Finger, L.W., Hazen R.M., Crystal structure and isothermal compression of Fe ₂ O ₃ , Cr ₂ O ₃ , and V ₂ O ₃ to 50 kbars Journal of Applied Physics, 1980. 51 : p. 5362-5368
Fe ₂ O ₃	Hill, A.H., Jiao F., Bruce P.G., Harrison A., Kockelmann W., Ritter C., Neutron Diffraction Study of Mesoporous and Bulk Hematite, α-Fe ₂ O ₃ . Chemistry of Materials, 2008. 20 : p. 4891-4899.
In ₂ O ₃	Prewitt, C.T., Shannon R.D., Rogers D.B., The C Rare Earth Oxide-Corundum Transition and Crystal Chemistry of Oxides Having the Corundum Structure. Inorganic Chemistry, 1969. 8 : p. 1985-1993.
La ₂ O ₃	Wu, B., Zinkevich M., Aldinger F., Wen D., Chen L., Ab initio study on structure and phase transition of A- and B-type rare-earth sesquioxides Ln ₂ O ₃ (Ln=La–Lu, Y, and Sc) based on density function theory. Journal of Solid State Chemistry, 2007. 180 : p. 3280-3287.
Mn ₂ O ₃	Norrestam, R., Ingri N., Östlund E., Bloom G., Hagen G., alpha-Manganese(III) Oxide --- a C-Type Sesquioxide of Orthorhombic Symmetry Acta Chemica Scandinavica, 1967. 21 : p. 2871-2884.
NiO	Shimomura, Y., Kojima M., Saito S., Crystal structure of ferromagnetic nickel oxide. Journal of the Physical Society of Japan, 1956. 11 : p. 1136-1146.
Sb ₂ O ₃	Whitten, A.E., Dittrich B., Spackman M.A., Turner P., Brown T.C., Charge density analysis of two polymorphs of antimony(III) oxide. Dalton Transactions, 2004. 7 : p. 23-29.
SiO ₂	Martinez, J.R., Palomares-Sanchez S., Ortega-Zarzosa G., Ruiz F., Chumakov Y., Rietveld refinement of amorphous SiO ₂ prepared via sol–gel method. Materials Letters, 2006. 60 : p. 3526–3529.
SnO ₂	Gracia, L., Beltrán A., Andrés J., Characterization of the high-pressure structures and phase transformations in SnO ₂ . A density functional theory study. The Journal of Physical Chemistry B, 2007. 111 : p. 6479-6485.
TiO ₂	Swamy, V., Dubrovinsky L.S., Dubrovinskaia N.A., Langenhorst F., Simionovici A.S., Drakopoulos M., Dmitriev V., Weber H.P., Size effects on the structure and phase transition behavior of baddeleyite TiO ₂ . Solid State Communications, 2005. 134 : p. 541–546.
V ₂ O ₃	Rozier, P., Ratuszna A., Galy J., Comparative structural and electrical studies of V ₂ O ₃ and V ₂ -xNi _x O ₃ (0<x<0.75) solid solution. Zeitschrift für Anorganische und Allgemeine Chemie, 2002. 628 : p. 1236-1242.
WO ₃	Woodward, P.M., Sleight A.W., Vogt T., Ferroelectric Tungsten Trioxide Journal of Solid State Chemistry, 1997. 131 : p. 9-17.
Y ₂ O ₃	Santos, C., Strecker K., Suzuki P.A., Kycia S., Silva O.M.M., Silva C., Stabilization of alpha-SIALONs using a rare-earth mixed oxide (RE ₂ O ₃) as sintering additive. Materials Research Bulletin, 2005. 40 : p. 1094-1103.
ZnO	Singhal, R.K., Samariya A., Xing Y.-T., Kumar S., Dolia S.N., Deshpande U.P., Shripathi T., Saitovitch E.B., <i>Electronic and magnetic properties of Co-doped Zn O diluted magnetic semiconductor</i> . The Journal of Alloys and Compounds, 2010. 496 : p. 324-330.
ZrO ₂	Naray-Szabo, S., <i>Zur Struktur des Baddeleyits ZrO₂</i> . Zeitschrift fuer Kristallographie, Kristallgeometrie, Kristallphysik, Kristallchemie, 1936. 94 : p. 414-416.

List of calculated quantum - mechanical descriptors

TABLE S3

Metal oxide	ΔH_f^c	TE	EE	Core	SAS	HOMO	LUMO	η	S	E_g	μ	E_v	E_c	χ^c	Hard	Shift	Ahof	Ad	Metal oxide
	kcal/mol	eV	eV	eV	A^2	eV	eV	eV	eV	eV	eV	eV	eV	eV	eV	eV	A^3	A^3	
Al ₂ O ₃	-600.0	-2755.8	-11997.7	9242.0	307.16	-8.53	1.66	-5.09	-0.10	-10.18	-3.44	1.66	-8.53	3.44	5.09	-3.44	17.83	17.79	Al ₂ O ₃
Bi ₂ O ₃	-148.5	-2864.3	-11242.7	8378.4	251.06	-9.43	-1.25	-4.09	-0.12	-8.18	-5.34	-1.25	-9.43	5.34	4.09	-5.34	19.92	19.84	Bi ₂ O ₃
CoO	-786.8	-5378.2	-45466.7	40088.5	347.56	-9.21	-5.67	-1.77	-0.28	-3.55	-7.44	-5.67	-9.21	7.44	1.50	-8.25	45.50	45.50	CoO
Cr ₂ O ₃	-235.3	-2507.8	-10028.3	7520.4	167.30	-8.25	-0.46	-3.89	-0.13	-7.79	-4.36	-0.46	-8.25	4.36	3.89	-4.36	16.35	16.02	Cr ₂ O ₃
Fe ₂ O ₃	-378.5	-3480.9	-13651.6	10170.7	172.57	-8.33	-0.09	-4.12	-0.12	-8.24	-4.21	-0.09	-8.33	4.21	4.44	-4.57	12.33	12.32	Fe ₂ O ₃
In ₂ O ₃	-52.1	-1961.0	-6085.1	4124.1	191.20	-10.62	-2.95	-3.84	-0.13	-7.68	-6.78	-2.95	-10.62	6.78	3.84	-6.78	12.44	12.43	In ₂ O ₃
La ₂ O ₃	-157.7	-2486.1	-8602.4	6116.2	232.92	-10.91	-2.00	-4.45	-0.11	-8.90	-6.45	-2.00	-10.91	6.45	4.45	-6.45	4.95	4.95	La ₂ O ₃
Mn ₂ O ₃	-96.3	-5269.3	-34774.7	29505.4	321.38	-5.02	-4.98	-0.02	-27.78	-0.04	-5.00	-4.98	-5.02	5.00	0.02	-5.00	734.03	40.97	Mn ₂ O ₃
NiO	68.0	-4671.0	-22764.2	18093.2	179.35	-7.78	-1.16	-3.31	-0.15	-6.62	-4.47	-1.16	-7.78	4.47	3.04	-4.37	21.35	21.23	NiO
Sb ₂ O ₃	-206.7	-2504.8	-10756.3	8251.5	255.24	-7.96	-0.96	-3.50	-0.14	-7.00	-4.46	-0.96	-7.96	4.46	3.50	-4.46	23.21	23.12	Sb ₂ O ₃
SiO ₂	-618.3	-2764.2	-10201.7	7437.6	262.92	-7.90	0.28	-4.09	-0.12	-8.18	-3.81	0.28	-7.90	3.81	4.09	-3.81	31.58	31.54	SiO ₂
SnO ₂	-266.6	-3511.0	-17713.0	14202.0	359.32	-6.97	-2.18	-2.40	-0.21	-4.79	-4.57	-2.18	-6.97	4.57	2.40	-4.57	34.22	34.14	SnO ₂
TiO ₂	-1492.0	-2782.9	-12685.1	9902.2	271.58	-7.08	-2.73	-2.18	-0.23	-4.36	-4.91	-2.73	-7.08	4.91	2.14	-4.33	49.54	24.94	TiO ₂
V ₂ O ₃	-139.5	-2168.1	-7623.9	5455.8	206.12	-5.81	-0.66	-2.58	-0.19	-5.15	-3.24	-0.66	-5.81	3.24	2.58	-3.24	26.36	26.22	V ₂ O ₃
WO ₃	-715.4	-4310.9	-21750.8	17439.9	302.37	-6.84	-6.61	-0.11	-4.41	-0.23	-6.73	-6.61	-6.84	6.73	0.11	-6.73	40.16	39.79	WO ₃
Y ₂ O ₃	-135.3	-2179.8	-9171.1	6991.3	636.97	-5.19	-1.51	-1.84	-0.27	-3.68	-3.35	-1.51	-5.19	3.35	1.84	-3.35	107.00	106.98	Y ₂ O ₃
ZnO	-449.4	-1320.2	-3221.7	1901.5	153.42	-11.36	-5.30	-3.03	-0.16	-6.07	-8.33	-5.30	-11.36	8.33	3.03	-8.33	9.09	9.07	ZnO
ZrO ₂	-638.1	-1331.3	-3510.7	2179.4	178.99	-10.92	1.03	-5.97	-0.08	-11.95	-4.95	1.03	-10.92	4.95	5.97	-4.95	10.74	10.71	ZrO ₂

List of calculated image descriptors

TABLE S4

Metal oxide	A	V	$d_s = \sqrt{\frac{A}{\pi}}$	$d_{V/m} = \sqrt[3]{\frac{6V}{\pi}}$	$d_{Sauter} = \frac{6V}{A}$	$A_{R,x} = \frac{d_{\min,x}}{d_{\max,y}}$	$A_{R,y} = \frac{d_{\min,y}}{d_{\max,x}}$	$P_x = \sum_{i=1}^n x_i - x_j $	$P_y = \sum_{i=1}^n y_i - y_j $	$\psi = \frac{\pi^{1/3} 6V^{2/3}}{A}$	$f_{circ} = \frac{4\pi A}{V^2}$	Metal oxide
	Area	Volume	Surface diameter	Volume/ mass diameter	Volume/surface diameter	Aspect ratio X	Aspect ratio Y	Porosity X	Porosity Y	Sphericity	Circularity	
	[px]	[px]	[(px) ^{1/2}]	[(px) ^{1/3}]	[-]	[-]	[-]	[px]	[px]	[(px) ^{1/3}]	[1/px]	
Al ₂ O ₃	1.11E+09	1.86E+06	1.88E+04	153	1.01E-02	0.568	0.072	5.15E+04	-3.16E+05	6.62E-05	4.00E-03	Al ₂ O ₃
Bi ₂ O ₃	9.80E+08	2.05E+06	1.77E+04	158	1.25E-02	0.402	0.055	-2.86E+05	-1.80E+05	7.94E-05	2.90E-03	Bi ₂ O ₃
CoO	1.14E+09	2.14E+06	1.90E+04	160	1.13E-02	0.429	0.061	2.11E+04	-2.42E+05	7.07E-05	3.10E-03	CoO
Cr ₂ O ₃	8.70E+08	1.52E+06	1.67E+04	143	1.05E-02	0.263	0.060	-3.42E+05	-5.51E+05	7.34E-05	4.70E-03	Cr ₂ O ₃
Fe ₂ O ₃	1.09E+09	1.78E+06	1.86E+04	150	9.80E-03	0.446	0.066	-1.18E+05	-3.18E+05	6.52E-05	4.30E-03	Fe ₂ O ₃
In ₂ O ₃	1.07E+09	2.04E+06	1.85E+04	157	1.14E-02	0.499	0.065	-1.68E+04	-2.81E+05	7.24E-05	3.20E-03	In ₂ O ₃
La ₂ O ₃	1.10E+09	1.91E+06	1.87E+04	154	1.05E-02	0.524	0.072	1.33E+04	-2.87E+05	6.79E-05	3.80E-03	La ₂ O ₃
Mn ₂ O ₃	1.09E+09	2.04E+06	1.86E+04	157	1.12E-02	0.479	0.064	7.57E+04	-2.46E+05	7.12E-05	3.30E-03	Mn ₂ O ₃
NiO	1.19E+09	1.96E+06	1.95E+04	155	9.90E-03	0.596	0.068	6.55E+03	-3.11E+05	6.36E-05	3.90E-03	NiO
Sb ₂ O ₃	9.60E+08	1.80E+06	1.74E+04	151	1.13E-02	0.241	0.055	3.49E+05	-3.72E+05	7.48E-05	3.70E-03	Sb ₂ O ₃
SiO ₂	9.70E+08	1.81E+06	1.76E+04	15	1.12E-02	0.421	0.065	1.25E+05	-4.13E+05	7.39E-05	3.70E-03	SiO ₂
SnO ₂	9.30E+08	1.68E+06	1.72E+04	148	1.09E-02	0.408	0.078	-6.23E+04	-4.28E+05	7.37E-05	4.10E-03	SnO ₂
TiO ₂	9.20E+08	1.77E+06	1.71E+04	150	1.16E-02	0.408	0.078	9.79E+03	-3.98E+05	7.70E-05	3.70E-03	TiO ₂
V ₂ O ₃	1.30E+09	2.20E+06	2.03E+04	161	1.02E-02	0.569	0.059	-5.81E+03	-2.20E+05	6.29E-05	3.40E-03	V ₂ O ₃
WO ₃	9.80E+08	1.72E+06	1.76E+04	149	1.06E-02	0.409	0.067	-1.67E+05	-4.30E+05	7.11E-05	4.10E-03	WO ₃
Y ₂ O ₃	1.28E+09	2.26E+06	2.02E+04	163	1.06E-02	0.633	0.058	1.02E+04	-1.89E+05	6.51E-05	3.10E-03	Y ₂ O ₃
ZnO	1.11E+09	1.95E+06	1.88E+04	155	1.05E-02	0.535	0.071	1.83E+03	-3.04E+05	6.80E-05	3.70E-03	ZnO
ZrO ₂	1.20E+09	2.22E+06	1.95E+04	162	1.11E-02	0.508	0.059	9.68E+03	-2.19E+05	6.86E-05	3.10E-03	ZrO ₂

* [px] - number of pixels

Name	Definition of image descriptor*
Descriptors reflecting nanoparticle size	Volume (V) The sum of all non-zero pixels episodes, combining measures of contour elements, assuming that the contour is a square with a side equal to the unity
	Surface diameter (d _s) The diameter of a sphere having the same surface area as the projected particle $d_s = \sqrt{\frac{A}{\pi}}$
	Equivalent volume diameter (d _v) The diameter of a sphere having the same volume as the projected particle $d_{v/m} = \sqrt[3]{\frac{6V}{\pi}}$
	Equivalent volume/surface (d _{sauter}) The diameter of a sphere having the same volume to surface ratio as the projected particle $d_{Sauter} = \frac{6V}{A}$
Descriptors reflecting nanoparticle surface area	Area (A) The sum of the all non-zero pixels (xi) $A = \sum_{i=1}^n (x_i)$
	Porosity (P _x) The sum of the relative differences in intensities between values of neighboring pixels (x _i and y _j) along the X axis $P_x = \sum_{i=1}^n x_i - x_j $
	Porosity (P _y) The sum of the relative differences in intensities between values of neighboring pixels (xi and yi) along the Y axis $P_y = \sum_{i=1}^n y_i - y_j $
Descriptors reflecting nanoparticle shape	Sphericity (ψ) The ratio of the surface area of a sphere - with the same volume as the particle considered - to the surface area of the particle $\psi = \frac{\pi^{1/3} 6V^{2/3}}{A}$
	Circularity (f _{circ}) The function of the surface area of the particle (A) and the particle's perimeter (V ²) $f_{circ} = \frac{4\pi A}{V^2}$
	Anisotropy ratio (AR _x) The ratio of the minimum length of chord of the X axis and the maximum length of chord of the Y axis. $AR_x = \frac{d_{\min,x}}{d_{\max,y}}$
	Anisotropy ratio (AR _y) The ratio of the minimum length of chord of the Y axis and the maximum length of chord of the X axis. $AR_y = \frac{d_{\min,y}}{d_{\max,x}}$

* Javad Sameni, Particle size analysis - Pharmaceutical material and product characterization. Available from: <http://www.authorstream.com/Presentation/javadsameni-231114-particle-size-analysis-pharmaceutics-particles-science-technology-ppt-powerpoint/> (accessed April 02, 2013).

Statistics for the model's coefficients

TABLE S5

		b_i	std. error	t-value	p-value
b₀	intercept	2.47	± 0.05	54.19	1.9 x 10 ⁻¹⁰
b₁	coefficient	0.24	± 0.05	5.08	1.4 x 10 ⁻³
b₂	coefficient	0.39	± 0.05	8.21	7.7 x 10 ⁻⁵

Results for internal validation with leave-one-out algorithm

TABLE S6

			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.1}	b_0	intercept	2.54	± 0.05	49.26	4.7×10^{-9}	0.90	0.13
	b_1	coefficient	0.14	± 0.06	2.52	4.5×10^{-2}		
	b_2	coefficient	0.41	± 0.06	7.30	3.4×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.2}	b_0	intercept	2.52	± 0.04	64.30	9.5×10^{-10}	0.95	0.10
	b_1	coefficient	0.24	± 0.04	5.85	1.1×10^{-3}		
	b_2	coefficient	0.41	± 0.04	9.76	6.7×10^{-5}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.3}	b_0	intercept	2.50	± 0.05	52.73	3.1×10^{-9}	0.93	0.12
	b_1	coefficient	0.26	± 0.05	5.23	2.0×10^{-3}		
	b_2	coefficient	0.41	± 0.05	8.11	1.9×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.4}	b_0	intercept	2.49	± 0.05	53.34	2.9×10^{-9}	0.94	0.11
	b_1	coefficient	0.23	± 0.05	4.72	3.3×10^{-3}		
	b_2	coefficient	0.40	± 0.05	7.96	2.1×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.5}	b_0	intercept	2.48	± 0.05	48.65	5.1×10^{-9}	0.93	0.13
	b_1	coefficient	0.26	± 0.05	4.76	3.1×10^{-3}		
	b_2	coefficient	0.40	± 0.05	7.46	3.0×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.6}	b_0	intercept	2.46	± 0.05	50.46	4.1×10^{-9}	0.94	0.12
	b_1	coefficient	0.26	± 0.05	5.05	2.3×10^{-3}		
	b_2	coefficient	0.42	± 0.05	8.06	2.0×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.7}	b_0	intercept	2.45	± 0.05	48.50	5.2×10^{-9}	0.93	0.12
	b_1	coefficient	0.24	± 0.05	4.46	4.3×10^{-3}		
	b_2	coefficient	0.42	± 0.05	7.82	2.3×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.8}	b_0	intercept	2.43	± 0.05	47.38	5.9×10^{-9}	0.92	0.13
	b_1	coefficient	0.26	± 0.05	4.69	3.4×10^{-3}		
	b_2	coefficient	0.37	± 0.05	6.73	5.2×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.9}	b_0	intercept	2.42	± 0.05	49.19	4.7×10^{-9}	0.93	0.12
	b_1	coefficient	0.26	± 0.05	4.93	2.6×10^{-3}		
	b_2	coefficient	0.41	± 0.05	7.84	2.3×10^{-4}		
			b_i	std. error	t-value	p-value	R^2	RMSE _c
Model CV-LOO _{.10}	b_0	intercept	2.37	± 0.05	52.40	3.2×10^{-9}	0.91	0.11
	b_1	coefficient	0.26	± 0.05	5.30	1.8×10^{-3}		
	b_2	coefficient	0.28	± 0.05	5.85	1.1×10^{-3}		

The results of the Y-scrambling test

FIGURE S1

Insubria plot

FIGURE S2