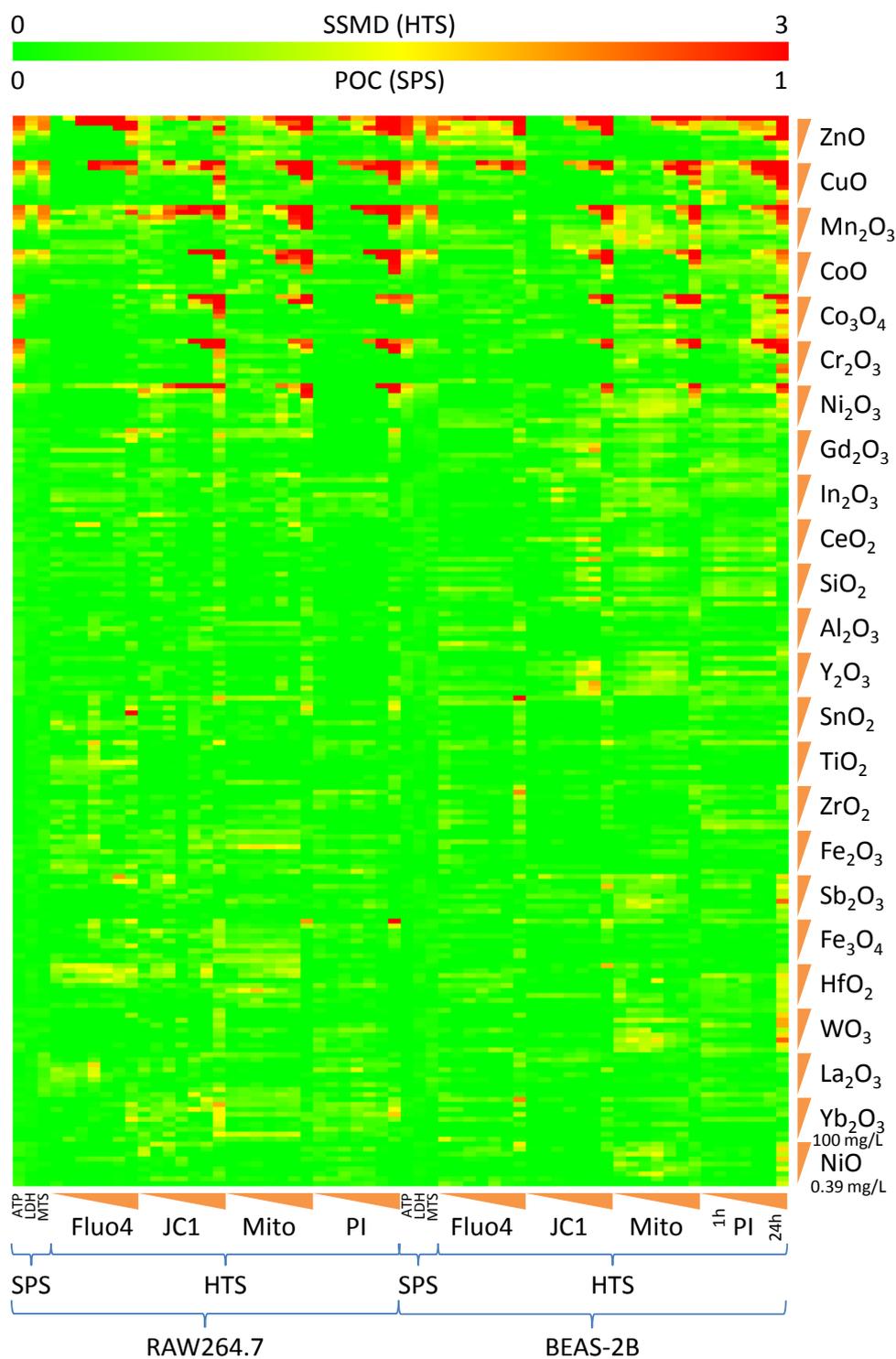**Supporting Information**

Figure S1. Toxicity of the NPs (exposure concentration: 0.39-100 mg/L, exposure time: 1-24h). SPS data were normalized as percent of control (POC) and the HTS data were normalized using the strictly standardized mean difference (SSMD). Higher POC/SSMD values indicate greater level of toxicity.
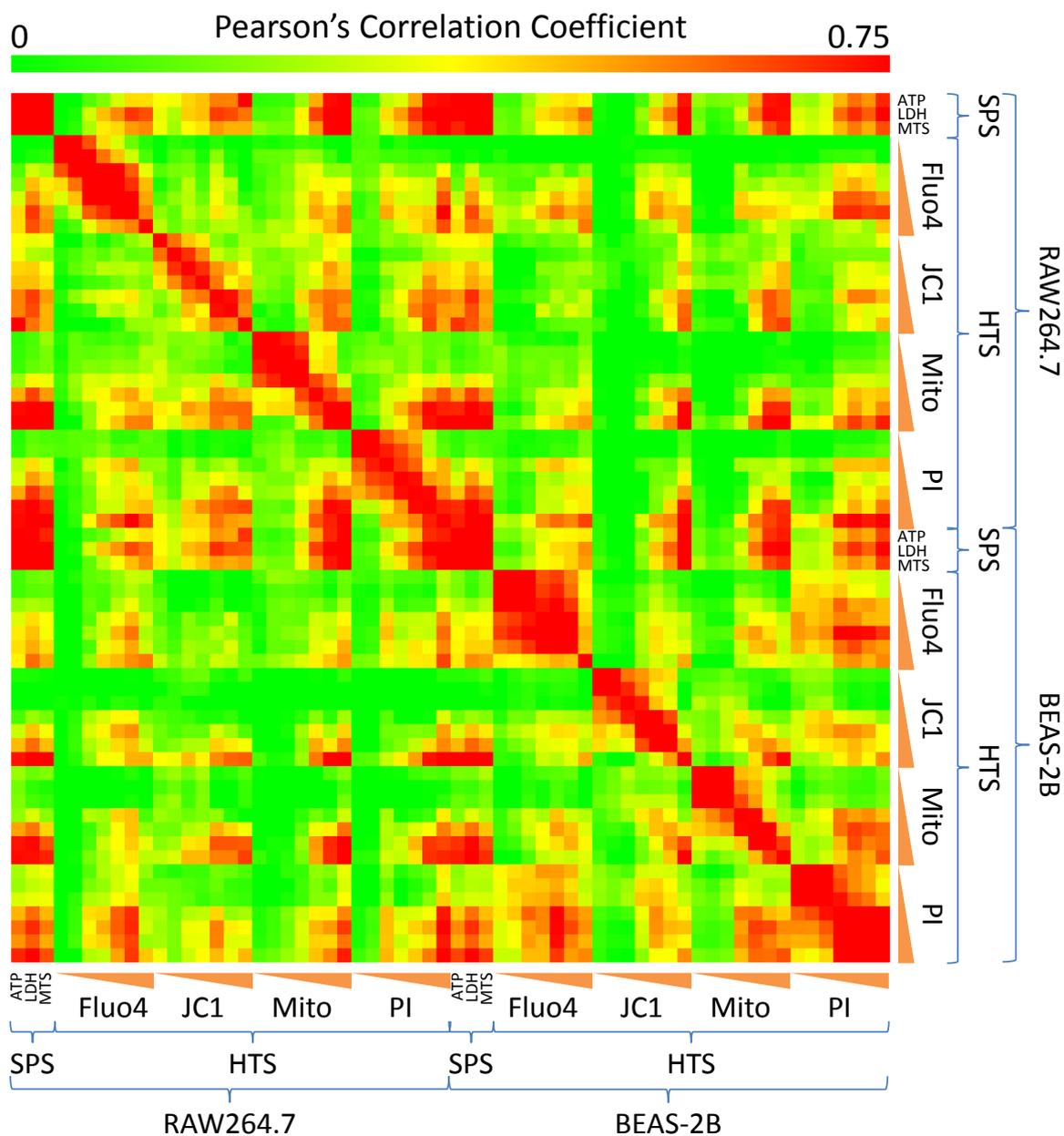
Figure S2. Pearson Correlation between different toxicity assays. A Pearson correlation coefficient (r) indicates a moderate positive linear correlation for $r = \sim 0.38\text{-}0.75$ and a strong positive linear correlation[22] for $r > 0.75$.
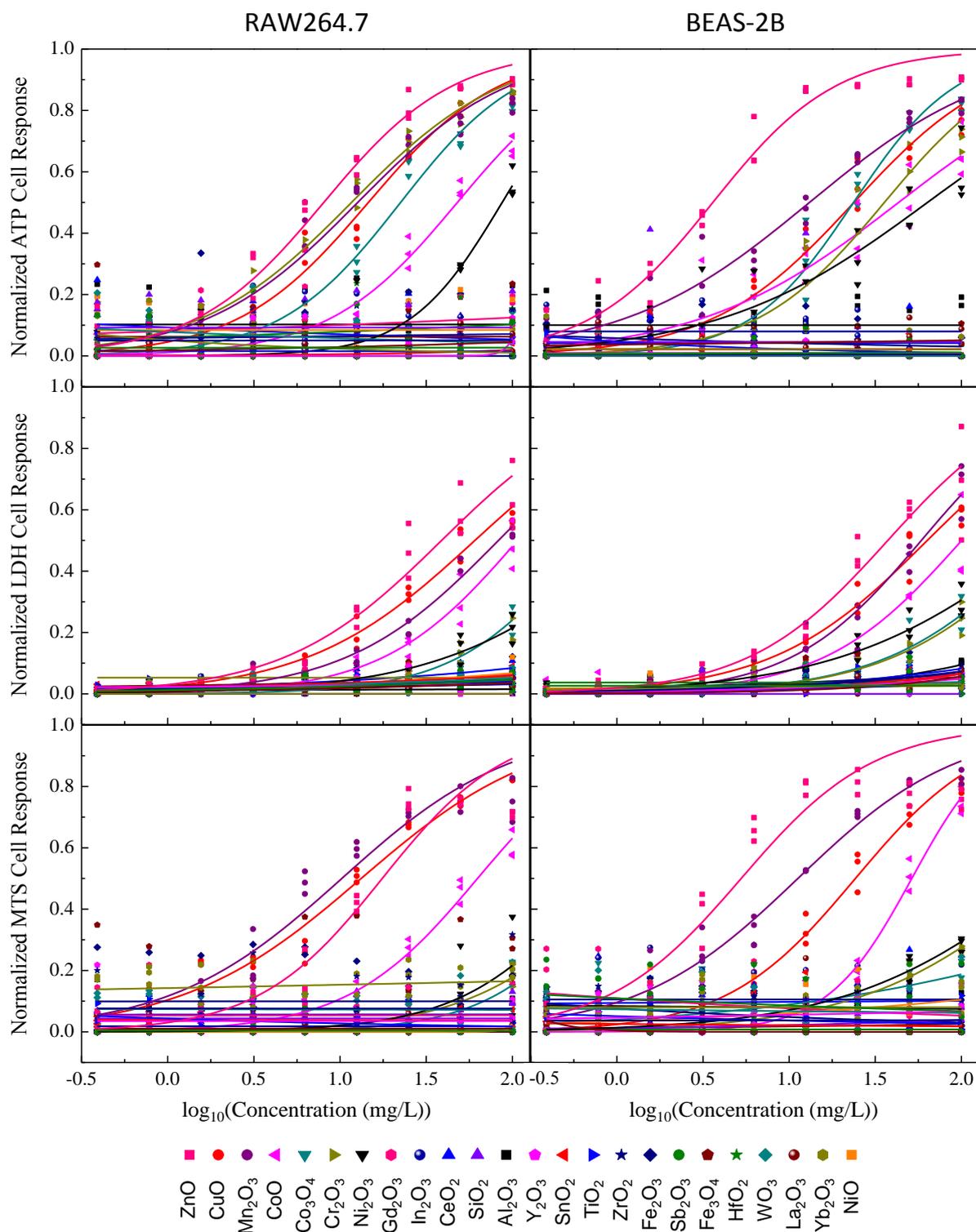
Figure S3. Dose-Response curves fitted to the SPS data (ATP, LDH, and MTS assays). A log-logistic function ($y = 1/(1 + 10^{s(\log_{10} EC50 - \log_{10} x)})$) was fitted to the NP induced cell responses (in triplicate) at each concentration (x)). The ZnO, CuO, Mn$_2$O$_3$, CoO, Co$_3$O$_4$, Cr$_2$O$_3$, and Ni$_2$O$_3$ NPs show clear dose-response behavior.

3

$$M^{2+}(g) \quad + \quad O^{2-}(g)$$

ΔH_{IE}
(Ionization energy)

$\Delta H_{EA}=-6.809$ eV
(Electron affinity)

ΔH_{Lat}
(Lattice energy)

$$M(g) \qquad O(g)$$

ΔH_{sub}
(Sublimation enthalpy)

$\Delta H_{Atm}=2.581$ eV
(Atomization energy)

ΔH_{sf}
(Formation enthalpy)

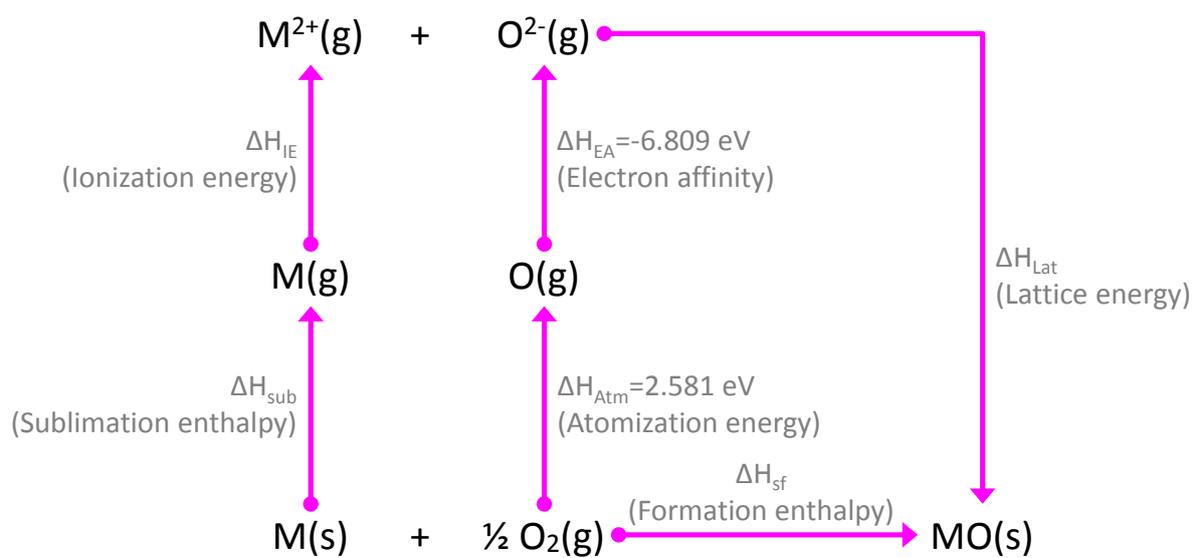$$M(s) \quad + \quad \tfrac{1}{2}\,O_2(g) \longrightarrow MO(s)$$

Figure S4. An illustration of Born-Haber Cycle[35] for metal oxide (MO). The symbols "s" and "g" identify solid and gas phases, respectively.

Oxidative stress

Energy to vacuum (eV)

-4.12

-4.84

Ec

Ec

Ec

e⁻

Ev

Ev

Ev

Biological redox potentials

Fe^{3+} transferrin/Fe^{2+} transferrin
$NADP^+$ / NADPH
Thioredoxin
SO_4^{2-} /HS^-
Oxidized / reduced glutathione
Fe^{3+} ferritin/Fe^{2+} ferritin
Cysteine/cystine
Fe^{3+}-citrate/Fe^{2+}- citrate
Fe^{3+}aq. H+/Fe^{2+}aq
Cytochrome c-Fe^{3+}/Cytochrome c -Fe^{2+}
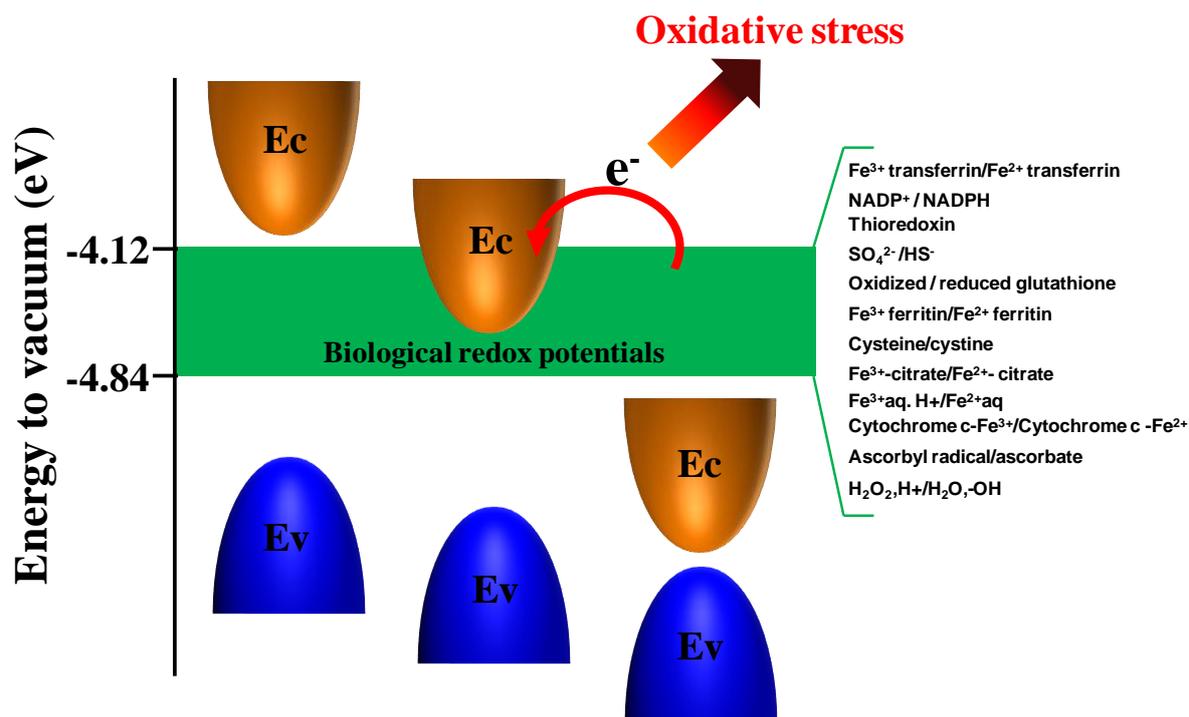Ascorbyl radical/ascorbate
H_2O_2,H+/H_2O,-OH

Figure S5. Conduction band energy as a factor of cellular oxidative stress generation. Electron transfer from biological material to NP might occur and lead to cellular oxidative stress generation if the NP's conduction band energy is within [-4.84, -4.12] eV (an estimated standard redox potentials of couples active in biological media with respect to the absolute vacuum scale)[36].
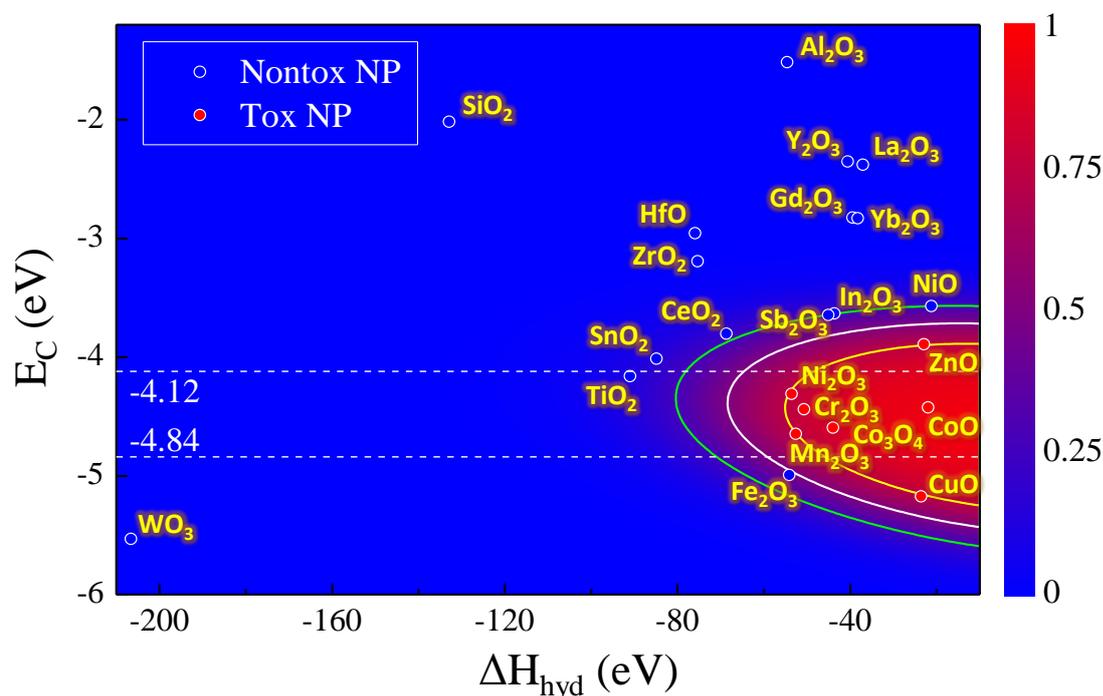
5

Figure S6. Toxicity probability of NP (x) belonging to the toxic class (T) given by the SVM based nano-SAR using conduction band energy (E_C) and hydration enthalpy (ΔH_{hyd}). The posterior toxicity probability $P(T|x)$ is depicted via the color map in the descriptor space. The middle contour, which is for $P(T|x)=0.5$, defines the nano-SAR classification boundary, while the inner ($P(T|x)=0.73$) and outer ($P(T|x)=0.27$) contours correspond to the decision boundaries for penalty ratios of false negative relative to false positive predictions (i.e., L_{FN}: L_{FP}) set as 1:2.7 and 2.7:1, respectively. The hydration enthalpy (ΔH_{hyd}) was estimated via Latimer's equation[a] ($\Delta H_{hyd}=-631.184Z^2/(r+50)$ eV). The nano-SAR classification accuracy was 93.2%. Note: For nano-SAR developed using a mix of reported experimental hydration enthalpy[b] values along with calculated values for those lacking experimental data (i.e., Co_3O_4, Ni_2O_3, Sb_2O_3, SiO_2, TiO_2, and WO_3), the classification accuracy is found to decrease to 90.2%.

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[a] Wulfsberg, G. *Principles of descriptive inorganic chemistry*. (University Science Books, 1991).
[b] Smith, D. Ionic hydration Enthalpies. *Journal of Chemical Education* **54**, 540-542 (1977).
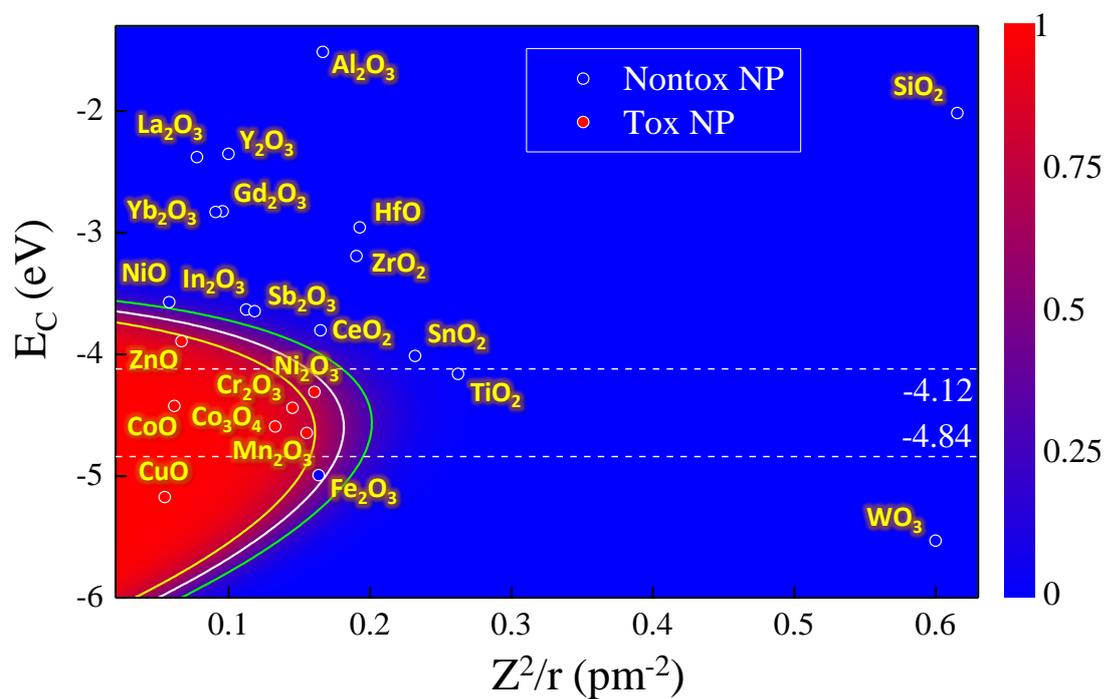
Figure S7. Toxicity probability of NP (x) belonging to the toxic class (T) given by the qLGR

based nano-SAR. The posterior toxicity probability P(T|x) is depicted in the color map in the

descriptor space. The middle contour for which P(T|x)=0.5 defines the nano-SAR

classification boundary, while the inner (P(T|x)=0.73) and outer (P(T|x)=0.27) contours

correspond to the decision boundaries for penalty ratios of false negative relative to false

positive predictions (i.e., L_{FN}: L_{FP}) set as 1:2.7 and 2.7:1, respectively.

Table S1. Descriptors (physicochemical properties) of the nanoparticles[a,b]

NP	dp	E_C	E_V	E_{Amz}	χ_{MeO}	ΔH_{sub}	ΔH_{IE}	ΔH_{sf}	ΔH_{Lat}	$\Delta H_{IE,1+}$	Z^2/r	IEP	ZP
	nm					eV					pm^{-2}	pH	mV
ZnO	22.6 ± 5.1	-3.891	-7.198	7.546	5.674	1.351	28.710	-3.608	42.928	9.394	0.0667	9.6	28.8
CuO	12.8 ± 3.4	-5.174	-6.515	7.719	5.874	3.497	31.515	-1.609	42.856	7.726	0.0548	7.9	7.6
Mn₂O₃	51.5 ± 7.3	-4.647	-7.635	11.709	5.919	2.936	59.677	-9.917	156.975	7.434	0.1552	3.7	-46.1
CoO	71.8 ± 16.2	-4.424	-6.832	9.454	5.735	4.422	29.387	-2.476	39.767	7.881	0.0615	9.2	21.6
Co₃O₄	10.0 ± 2.4	-4.593	-7.025	10.755	5.927	4.422	46.137	-9.380	99.573	7.881	0.1329	9.4	24.6
Cr₂O₃	193.0 ± 90.0	-4.439	-7.524	13.920	5.858	4.120	58.331	-11.717	158.322	6.767	0.1452	5.3	-32.6
Ni₂O₃	140.6 ± 52.5	-4.309	-7.688	11.709	6.052	4.458	65.455	-5.073	164.157	7.639	0.1607	8.3	32.2
Gd₂O₃	43.8 ± 15.8	-2.825	-8.102	16.782	5.499	4.120	42.989	-18.820	134.692	6.150	0.0957	8.0	6.5
In₂O₃	59.6 ± 19	-3.632	-7.322	11.188	5.583	2.518	55.204	-9.606	144.351	5.786	0.1125	9.2	61.9
CeO₂	18.3 ± 6.8	-3.803	-7.450	20.121	5.650	4.354	77.697	-11.284	99.775	5.539	0.1649	7.8	21.4
SiO₂	13.5 ± 4.2	-2.018	-11.118	18.734	6.190	4.664	107.795	-9.410	136.029	8.151	0.6154	1.0	-31.8
Al₂O₃	14.7 ± 5.2	-1.515	-9.815	15.872	5.665	3.429	56.691	-17.345	164.955	5.985	0.1667	7.4	0.0
Y₂O₃	32.7 ± 8.1	-2.352	-8.201	17.433	5.406	4.402	43.362	-19.748	131.676	6.217	0.1000	9.6	42.7
SnO₂	62.4 ± 13.2	-4.013	-8.013	14.397	5.812	3.122	96.334	-5.986	122.369	7.344	0.2319	4.0	-38.8
TiO₂	12.6 ± 4.3	-4.161	-7.491	19.775	5.767	4.902	96.063	-9.779	125.924	6.828	0.2623	6.4	-19.4
ZrO₂	40.1 ± 12.6	-3.192	-8.233	22.723	5.618	6.322	83.379	-11.252	115.954	6.634	0.1905	5.8	-12.8
Fe₂O₃	12.3 ± 2.9	-4.993	-6.987	12.489	5.978	4.306	59.047	-8.512	148.300	7.903	0.1636	7.2	-2.1
Sb₂O₃	11.8 ± 3.3	-3.645	-8.138	10.408	5.514	2.740	53.278	-7.346	142.071	8.608	0.1184	1.0	-35.3
HfO₂	28.4 ± 7.3	-2.956	-8.371	23.938	5.705	6.409	84.863	-1.170	104.812	6.825	0.1928	8.1	33.5
WO₃	16.6 ± 4.3	-5.532	-8.586	24.978	6.640	8.820	213.421	-8.734	250.324	7.864	0.6000	0.3	-61.3
Yb₂O₃	61.7 ± 11.3	-2.831	-7.933	15.091	5.429	1.613	45.092	-18.807	138.672	6.254	0.0909	8.2	9.9
La₂O₃	24.6 ± 5.3	-2.380	-8.147	17.433	5.378	4.467	40.280	-18.668	129.054	5.577	0.0776	9.4	54.3
NiO	13.1 ± 5.9	-3.570	-7.445	9.454	5.744	4.458	30.266	-2.494	40.503	7.639	0.0580	11.4	27.6

[a] d_p: primary nanoparticle (NP) size (given in the format of average size (d) ± standard deviation (σ)), E_C: NP energy of conduction band, E_V: NP energy of valence band, E_{Amz}: metal oxide atomization energy, χ_{MeO}: metal oxide electronegativity, ΔH_{sub}: metal oxide

sublimation enthalpy, ΔH_{IE}: metal oxide ionization energy, ΔH_{sf}: metal oxide standard molar enthalpy of formation, ΔH_{Lat}: metal oxide lattice enthalpy, $\Delta H_{IE,1+}$: first molar ionization energy of metal, Z^2/r: ionic index of metal cation; IEP: NP isoelectric point, ZP: NP zeta potential in water at PH of 7.4; E_{Amz} was converted from the atomization energy in kcal/eqv. The atomization energy of Ni_2O_3 is lacking and thus was estimated as that of Mn_2O_3 since they share the same molecular structure and the atomization energies of NiO and MnO are identical. Note that the enthalpies involved in Born-Haber cycle for Co_3O_4 were calculated by taking the average of those for CoO and Co_2O_3. Also, the Ionic index of the metal ion in Co_3O_4 was estimated as the weighted average (1:2) of Co^{2+} and Co^{3+} in the metal oxide NP crystal.

[b]Thirty descriptors were used for nano-SAR development. Fourteen of the descriptor values are provided in the Table, while the remaining 16 can be easily calculated as described below.

i. Seven descriptors based on primary NP size were evaluated for SAR development, including: different orders of average size (d^2, d^1, d, d^2), standard deviation (σ), mean/standard deviation ratio (d/σ), and coefficient of variation (σ/d);

ii. Three other quantum mechanics descriptors were derived from E_C and E_V, including chemical potential ($\mu=(E_C+E_V)/2$), chemical hardness ($\eta=(E_C-E_V)/2$), and electrophilicity ($\omega=\mu^2/2\eta$);

iii. Fundamental metal oxide descriptors were also included in the initial pool of descriptor, including numbers of metal and oxygen atoms, atomic mass of metal and metal oxide molecular weight, group and period of metal (in periodic table), and electronegativity of metal; these are not listed in the above table as they can be easily ascertained from the metal oxide chemical formula.