Importance of Doping, Dopant Distribution, and Defects on Electronic Band Structure Alteration of Metal Oxide Nanoparticles: Implications for Reactive Oxygen Species

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Abstract

Nano-scale metal oxide particles are considered to have the potency to generate reactive oxygen species (ROS), one of the key mechanisms underlying nanotoxicity. However, the nanotoxicology literature demonstrates a lack of consensus on the dominant toxicity mechanism(s) for a particular metal oxide nanoparticle (MONP). Moreover, recent literature has studied the correlation between band structure of pristine MONPs to their ability to introduce reactive species and thus has downplayed the ROS-mediated toxicological relevance of a number of such materials. On the other hand, material science can control the band structure of these materials to engineer their electronic and optical properties and thereby is constantly modulating the pristine electronic structure. Since band structure is the fundamental material property that controls ROS-producing ability, band tuning via introduction of dopants and defects needs careful consideration in toxicity assessments. This commentary critically evaluates the existing material science and nanotoxicity literature and identifies the gap in our understanding of the role of important crystal structure features (i.e., dopants and defects) on MONPs' electronic structure alteration as well as their ROS-generation capability. Furthermore, this commentary provides suggestions on characterization techniques to evaluate dopants and defects on the crystal structure and identifies research needs for advanced theoretical predictions of their electronic band structures and ROS-generation abilities. Correlation of electronic band structure and ROS will not only aid in better mechanistic assessment of nanotoxicity but will be impactful in designing and developing ROS-based applications ranging from water disinfection to next-generation antibiotics and even cancer therapeutics.

Keywords: Band gap, nano-defects, nanotoxicity, nano-imperfections.

1. Introduction

Metal oxide nanoparticles (MONPs) are one of the most prepared and used engineered nanomaterials with applications in electronics, optical devices, medical processes and devices, catalysis, alternative energy production, and environmental remediation and as antimicrobial sprays and coatings (Murphy et al., 2005). Manufacturing processes, and end-of-life disposal events for these applications might serve as exposure pathways to humans and the natural environment and thus raise concerns for eco- and nano-toxicity (Klaine et al., 2008; Nel et al., 2006; Saleh et al., 2015). The key mechanisms for toxicity from MONPs include dissolved ions, alteration of redox potential and subsequent catalytic reaction, and reactive oxygen species (ROS) and their interaction with biological entities (Aich et al., 2014; Ju-Nam and Lead, 2008; Saleh et al., 2015; Sarkar et al., 2014; von Moos and Slaveykova, 2014).

ROS, e.g., singlet oxygen, hydrogen peroxides, and superoxides, are known to cause toxicological stress to cells via alteration of redox-mediated cellular processes and damage to cell-membranes and other cellular components (Nel et al., 2006; Saleh et al., 2014; von Moos and Slaveykova, 2014). Some of the key interactions include lipid peroxidation leading to disruption of the cell-membrane (Nel et al., 2006), protein oxidation resulting in imbalance of enzymatic activities (Kumar et al., 2011), nucleic acid oxidation followed by genetic mutation and developmental toxicity (Nel et al., 2006). The free radicals can participate in membrane protein remodeling, both in prokaryotic and eukaryotic cells, to alter permeability through the membranes (Pacurari et al., 2011; Zhang et al., 2010). The radicals also can reduce the production of natural antioxidants such as glutathione, superoxide dismutase, and catalase (von Moos and Slaveykova, 2014).

Generation of these reactive species occurs by electron transfer from the MONP surfaces, initiated by the energetic positioning of the electronic bands (Figure 1) as indicated by recent

literature (Burello and Worth, 2011; Gajewicz et al., 2015; Kaweeteerawat et al., 2015; Zhang et al., 2012). Fundamental electronic structure and distribution of metals control the electronic band positioning. However, imperfections at the nano-scale (Janotti and Van de Walle, 2007; Laks et al., 1991) and introduction of secondary metals as dopants (Buonsanti and Milliron, 2013), further modulate the band structure (Figure 2). Such modulation can either be incidental (during synthesis) or engineered (to extract desired electronic properties) and both can contribute to an altered ability to generate ROS. Furthermore, the confounding conclusions about the key mechanisms of MONP nanotoxicity (Djurišić et al., 2015; von Moos and Slaveykova, 2014) should consider crystal defects and dopants due to, their ability to generate a wide range of ROS. Identifying the thermodynamic favorability of dopant or defect mediated ROS-generation by MONPs will eventually enabled screening of MONPs for ROS-generation kinetics. However, the effects of unintentional nano-scale imperfections or intentional defects and dopant distribution of MONPs on their ROS-generation ability have not been systemically evaluated in most nanotoxicity studies. This commentary focuses on band structure alteration of doped and defected MONPs and discusses the toxicological consequences and potential future strategies to better characterize lattice defects and dopants.

2. Mechanisms of metal oxide nanoparticle toxicity

Nanotoxicity of a large set of metal oxide (e.g., TiO₂, CuO, ZnO, cerium oxide (CeO₂), iron oxide (Fe₂O₃), manganese oxide (Mn₂O₃)) particles has been assessed, and quantitative structure activity relationship (QSAR) models on ROS and band gap (Kaweeteerawat et al., 2015; Zhang et al., 2012), hydration energies (Kaweeteerawat et al., 2015), or enthalpy of formations (Gajewicz et al., 2015) have been proposed. Despite such promising advances, conflicting reports regarding the dominant mechanism of toxicity continues to surface for most MONPs, while consensus

exists for the ROS-mediated toxicity due to nano-scale TiO₂ (Bar-Ilan et al., 2012; Djurišić et al., 2015). For example, some reports on ROS control of ZnO (a photocatalyst) toxicity (Kaweeteerawat et al., 2015; Kumar et al., 2011; Li et al., 2014; Sharma et al., 2012) conflict with the dominant mechanisms of dissolution and particle-cell interaction that are reported elsewhere (Buerki-Thurnherr et al., 2013; Chusuei et al., 2013; Song et al., 2010; Zhang et al., 2012), where the latter ones (Buerki-Thurnherr et al., 2013; Chusuei et al., 2013; Song et al., 2010; Zhang et al., 2012) mention that particle-induced ROS was not playing a significant role in ZnO nanotoxicity. Other MONPs, including CuO, CeO₂, and Mn₂O₃, showed similar contradiction (Table 1) in dominant toxicity mechanisms (Djurišić et al., 2015). The sources and synthesis techniques of the MONPs for these studies varied widely (Table 1), with no reported assessment of MONP band structure. Differences in synthesis techniques (for the same MONP) introduce differences in crystal defects and dopants. For example, nitrogen-doped TiO₂ contained a higher dopant concentration in the crystal structure and consequently higher visible light activity when urea was used as the nitrogen source as compared to the usage of molecular nitrogen or inorganic nitrogenous compounds (Rehman et al., 2009). Use of nitrous oxide (N₂O), on the other hand, can cause a higher degree of transformation from anatase to rutile structures (Guo et al., 2007). Moreover, the presence or absence of post-synthesis annealing also is known to contribute to the extent and types of defects present in ZnO nanorods, modulating their photocatalytic activities (Das et al., 2014). It is thus probable that these MONPs, synthesized via a multitude of techniques, ranged widely in band structure as a result of defects and doping; consequently, differences in band structure might have resulted in variations in their manifested toxicity (Djurišić et al., 2015). Other bio-related differences (e.g., media choice, bacterial strains, assay type) might also contribute to the lack of clarity in identifying the dominant mechanism of nanotoxicity. However, the role of crystal defect and dopant variation in ROS generation cannot

be ignored. Systematic characterization of defects and dopants in MONPs is critical to assess the ability of these materials to generate ROS; then, inconsistencies among various studies regarding the role of ROS in the toxicity of a particular MONP can be resolved.

3. Metal oxide nanoparticle band structure and ROS

Band gap engineering and tuning the energetic levels at band edges are at the forefront of materials science, motivated by energy conversion and other electronic applications (Aich et al., 2014; Buonsanti and Milliron, 2013; Chen et al., 2004; Norris et al., 2008; Schimpf et al., 2012). The band gap energy (E_g) of a material is determined by the positions of the valence band (E_v) and conduction band (E_c) edges (Figure 1). Energetic activation of metal oxide and other semiconductor nanomaterials, for example by light irradiation, enables excitation of electrons from E_v to E_c ; this results in the presence of excess of electrons in the conduction band and empty states or presence of electropositive ‘holes’ in the valence band (Figure 1)(Brunet et al., 2009). Conduction band electrons at E_c can act as strong reducers to react with oxygen molecules to produce the superoxide anion ($O_2^{\cdot-}$), which can then act as a precursor for production of hydroxyl radicals ($\cdot OH$) and singlet oxygen (1O_2). On the contrary, the holes (with their high oxidizing ability) can react with water or hydroxyl ions to produce hydroxyl radicals ($\cdot OH$) (Figure 1) (Burello and Worth, 2011). These ROS can then interact with biological entities, resulting in toxicity. To understand the ROS generation and relevant toxicity of these MONPs, the redox potentials of these different ROS have been correlated with different MONP electronic structures. It has been shown that metal oxides with E_c positioning within the cellular redox potential (CRP; -4.12 to -4.84 eV) allows for ROS generation to occur in aqueous medium (Burello and Worth, 2011). This paradigm has been validated by testing a range of MONPs, where the relative

positioning of their E_c with the CRP was correlated with observed toxicological endpoints (Kaweeteerawat et al., 2015; Li et al., 2012; Zhang et al., 2012).

The hypothesis that E_c positioning of the pristine MONP with respect to the CRP will control MONP's ROS-generation abilities might hold true from an electrochemical perspective, if defect and dopant-free MONPs can be synthesized at the nano-scale. However, to synthesize (by grinding, thermal, colloidal, microwave, annealing techniques) of a rather perfect, i.e., defect-free, metallic nano-structure is not trivial and is rather uncommon (Janotti and Van de Walle, 2007; McCluskey and Jokela, 2009; Merz et al., 2011). Inherently defective nano-crystals are rather common to find in a synthesized MONP batch, where the defect distribution is also likely to vary between the batches. On the contrary, deliberate introduction of defects, as in doping metal oxides to obtain n-type and p-type structures or to tune the band gap for light absorption, is common in band gap engineering (Buonsanti and Milliron, 2013; Lounis et al., 2014b; Norris et al., 2008). Defects and dopants are known to alter the band structure (Janotti and Van de Walle, 2006; Lounis et al., 2014b; Norris et al., 2008), leading to deviations in E_c positioning as compared to the pristine MONP band structure. Band bending and E_c band edge shifts should be carefully measured and reported because such changes might give some MONPs the capability to produce ROS, thereby becoming eco- and nano-toxicologically relevant. For instance, indium oxide (In_2O_3) and ZnO (Zhang et al., 2012), where the E_c positioning in their pristine states does not fall within the CRP range, will undergo E_c band shift upon introduction of dopants. Examples of such doped materials are Sn-doped In_2O_3 (Lounis et al., 2014a; Schimpf et al., 2014b), Mn-doped ZnO (Bhat and Deepak, 2005), Ce-doped ZnO (Faisal et al., 2013). Comprehensive literature reviews discuss the effects of synthesis techniques or doping strategies on alteration of crystal structure, electronic properties, and catalytic response of MONPs (Buonsanti and Milliron, 2013; Djuricic et al., 2014; Kumar and Rao, 2015; Pan et al., 2013; Zhang and Lin, 2012). A

careful evaluation of the importance of nano-defects and dopants in band gap alteration is thus essential.

4. Role of doping, dopant distribution, and defects on band structure

Doping of metal oxides is commonly pursued to attain improved electronic, optical, and catalytic performance (Chen et al., 2011; Garcia et al., 2011). The major mechanism behind such property tuning is to achieve control over doping (Figure 2) that alters electron transfer characteristics via changes in crystalline structure of the pristine MONP (Buonsanti and Milliron, 2013; Lounis et al., 2014a). Such changes lead to band gap narrowing or expansion, resulting in shifted E_c positioning. For example, TiO_2 is a commonly used photocatalyst that shows a reduction in band gap when doped with non-metals (e.g., N, C, S), transition metals (e.g., Fe, Cu, Ni, Cr, Pt), or noble metals (e.g., Pt, Au, Ag, Ru) (Pelaez et al., 2012). While undoped TiO_2 is only photoactive in the UV range, doping-induced band gap narrowing enables it to become photocatalytic and to generate ROS under visible irradiation. This becomes possible due to changes in lattice parameters or dopants acting as electron traps preventing charge recombination, or due to an intermediate energy level introduced between the conduction and valence bands. Similarly, doping-induced band bending also is observed in Mn-doped ZnO (Bhat and Deepak, 2005) or Sn-doped In_2O_3 (Lounis et al., 2014a), thus, increasing the ROS-generation ability as compared to their undoped counterparts. In many cases, such doping-induced conduction band edge shifts occur due to disruption of the lattice structure of the parent metal oxides by the dopants (e.g., Sn in case of Sn-doped In_2O_3). This results in an irreversible perturbation of the electronic structure and hence changes electron densities in the conduction band (Schimpf et al., 2014a). However, all these changes are dependent on the extent of doping and on dopant distribution (Bhat and Deepak, 2005; Lounis et al., 2014a; Lounis et al., 2014b; Schimpf et al., 2014a).

Alongside doping, variations in synthesis techniques and the annealing process can control imperfections in crystalline NPs, which then results in band structure alteration. Size and shape-specific MONPs are generally obtained via vapor deposition (Polarz et al., 2005; Xing et al., 2003), aqueous solution based growth (Tam et al., 2006), electrodeposition (Sauer et al., 2002), or via top-down approach such as milling of bulk metallic particles (Fecht, 1995). The bottom-up processes involve nucleation of dissolved ions in the presence of a substrate (or seed), that proceeds toward ‘ripened’ crystal structures (Leach et al., 2007). Depending on the substrate or precursor, temperature, gas pressure, post-synthesis annealing, and other such synthesis parameters, the crystal lattice ordering can vary significantly and the resulting strain leads to formation of defects (Devan et al., 2012; Schmidt-Mende and MacManus-Driscoll, 2007; Wang et al., 2008). In the case of metal oxides, variations in oxygen pressure, i.e., the ratio of precursor to oxygen during nucleation and growth stages, can control the extent of oxygen vacancies in the crystal structures (Liu et al., 2004). These imperfections lead to loss or gain of electrons from the conduction band, thereby, altering the electronic properties (Asthana et al., 2011; Ischenko et al., 2005; Janotti and Van de Walle, 2006). For example, wet chemical synthesis can lead to a reduction in the band gap of ZnO (e.g., E_g of -2.9 eV for wet-synthesized vs. -3.22 eV for annealed) because of the surface defects present (Asthana et al., 2011). Similarly, biogenic or modified hydrothermal annealing of CeO₂ nanostructures can lead to increases in Ce³⁺ and oxygen vacancies, resulting in band gap narrowing and photocatalysis via visible irradiation (Ansari et al., 2014; Lawrence et al., 2011). Top-down approaches, on the other hand, involve high energy input via mechanical attrition and non-uniform stress on the ground particles, which result in atomic shifts or dislocations from lattice or surfaces (Fecht, 1995; Leach et al., 2007) leading to alterations in electronic properties. For instance, synthesis of ZnO via grinding (with different capping agents) has shown to control oxygenated defect sites, thereby modulating their

band gap (Jitti-a-Porn et al., 2011). Further, TiO₂ band gap reduction through intentional defect engineering of pre-synthesized nanostructures has been achieved using electron-beam-assisted synthesis techniques (Khan et al., 2014a). Chemically bound surfactant or polymeric surface coatings or capping agents can reduce defects or imperfections on nanocrystal surfaces (Lakshmi Prasanna and Vijayaraghavan, 2015). The nature of bond formation on defect alteration need to be studied systematically to assess the role of coatings on electronic structure alteration.

5. Nanotoxicological implications

A few MONPs are known to produce ROS, driven by the inherent positioning of their E_c band lying within the range of the CRP; these include TiO₂, nickel oxide (Ni₂O₃), cobalt oxides (CoO and Co₃O₄), chromium oxide (Cr₂O₃), and Mn₂O₃ with E_c positions at -4.16, -4.31, -4.42, -4.59, -4.44, and -4.65 eV, respectively. The E_c position for other important MONPs are beyond the CRP range, namely In₂O₃, ZnO, and CuO, and are not considered as critical MONPs from an environmental health and safety (EHS) perspective because of their assumed lack of ROS generation (Zhang et al., 2012). However, doping and defects will alter their band structure, thereby potentially allowing the E_c level to fall within the CRP.

In₂O₃ doped with Sn could be one such case where the MONPs might become ROS-active upon doping. The E_c positioning of In₂O₃ as independent metal oxide is outside the CRP range, and thus is considered as less toxic MONPs (Lison et al., 2009; Zhang et al., 2012). However, upon doping with Sn, the conduction band of In₂O₃ bends as a function of the dopant distribution and concentration (Gilstrap, 2009; Lounis et al., 2014a). Recent reports suggest that extracellular and intracellular ROS production will occur from Sn-doped In₂O₃, which has resulted in oxidative stress in zebra fish embryos (Brun et al., 2014; Lison et al., 2009). Similarly, while ZnO photocatalysts showed little antibacterial activity (E_c outside of the CRP), Fe- (2.1%) and Mn-

(0.8%) doped ZnO resulted in elevated ROS generation and caused increased cytotoxicity (Yin and Casey, 2014), likely via band gap modulation and E_c repositioning within CRP (Figure 1) (Bharati et al., 2012; Hoque et al., 2014). Moreover, distribution, types, and concentrations of native point defects (e.g., oxygen vacancies) in nano-scale ZnO (Guo et al., 2011; Wang et al., 2012a; Zhang et al., 2014) also have shown to contribute to band gap alterations. A simple sonication-based technique has been used to induce defects in ZnO to enhance photoelectrochemical water splitting by band gap reductions (Wang et al., 2013). Similarly, CeO_2 , which is located far outside of the CRP- E_c range and identified as a non-ROS generator (Zhang et al., 2012), has been shown to undergo band gap reduction and conduction-band modulation to achieve enhanced visible light activity and ROS production (Ansari et al., 2014; Khan et al., 2014b; Lawrence et al., 2011). Defect-mediated toxicological responses have been observed for Ag nanoparticles, which could not be completely explained by a dissolution-based mechanism (George et al., 2012). Since unintentional crystal defects and intentional band gap engineering controls the band structure of these materials, it is important to develop strategies for systematically assessing the role of doping and defects on the ability of this wide material class to generate ROS.

This commentary highlights that band structure alteration will result from dopants and defects in the nano-structure. The distribution and position of the dopants and defects will influence the electronic band properties. The nanotoxicology community assesses nanomaterial safety using materials synthesized with a wide variety of techniques. Defect incorporation and foreign atom introduction are highly probable in the MONP samples studied for safety assessment. Moreover, band gap engineering is precisely involved in modulation of band structure to attain the desired electronic properties for their applications. Further, band-engineered MONPs released from electronic or medical processes/devices might undergo transformation via

dissolution, reaction, or photo-activation; which will alter the crystal structure of the particle surface and add to the defects and dopant distribution complexity. Use of standard ROS assays can be employed to differentiate the ROS-generation ability of MONPs with variable band-structures originating from controlled defect-engineering and doping. However, since ROS assays are average and overall measures, the sample of MONP with no control over crystal defects and dopants could produce inconsistent conclusion on ROS generation potency, depending on the degree of heterogeneity of these properties within the samples tested. Thus synthesizing MONPs with a high degree of control over these crystal lattice attributes (i.e., defects and dopants) is essential to systematically assess ROS-mediated MONP toxicity. Collaboration between the nanotoxicology and material science communities is thus necessary.

6. Mechanistic strategies for atomistic MONP characterization

What strategies can nanotoxicologists and material scientists undertake to expedite the safety assessment of ROS-active MONPs? To-date, the material science field has not developed a predictive tool that can accurately capture the band structure of a nanomaterial based on its pristine composition. Recently, notable efforts have been made to achieve theoretical predictability on band structure alteration by dopants and defects (Anderson and Chris, 2009; Andriotis and Menon, 2015); however, continued and systematic research is necessary to evaluate the role of dopant atoms' positioning (surface dopants vs. distributed) (Goings et al., 2014) in band structure modulation as well as its relationship to the ROS-generation-ability of MONPs. Such theoretical development can simplify the job of the nanotoxicology community to narrow down the important MONPs from the large set of ROS-active materials. Such predictability can be complemented with careful synthesis of MONPs possessing precise defects and dopant content and distribution. National Institute of Standards and Technology (NIST) might get involved in

such efforts, possibly preparing such MONP standards with controlled dopants and defects; such materials could then be utilized to systematically assess their ROS-mediated nanotoxicity. Furthermore, rigorous and detailed characterizations of dopants and/or defects also are critical. Such characterization can be performed with X-ray diffraction (Wang et al., 2006), nano beam diffraction with high-angle annular dark field scanning transmission electron microscopy (HAADF-STEM) (Ward et al., 2014), slow positron beam spectroscopy (Xue et al., 2013), photoluminescent (PL) emission (Sekiguchi et al., 2000; Zhang et al., 2014), X-ray absorption spectroscopy (XAS) (Brown and Parks, 2001; Rossi et al., 2014; Waychunas and Zhang, 2008), X-ray standing wave measurements (Zhang et al., 2004), and X-ray spectromicroscopy (STXM) (Chen et al., 2014; Myneni et al., 1999; Warwick et al., 1998). Not only material scientists but also nanotoxicologists can add these characterization tools to the routine assessment sequence, depending on the ROS-generation ability of the MONPs (predicted or characterized by the material scientists). Nanotoxicologists on the other hand can continue to develop and utilize the power of high throughput assays to scan across a large material set to identify highly ROS-producing MONPs. Such initial screening techniques can then be utilized to develop standard materials (with controlled dopants and defects) of the most ROS-active MONPs. Systematic assessment of the role of dopants and defects are necessary to resolve mechanistic controversies on ROS-mediated MONP toxicity.

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References

322 Aich N, Plazas-Tuttle J, Lead J, Saleh N. A Critical Review of Nanohybrids: Synthesis, Applications, and
 323 Environmental Implications. *Environmental Chemistry* 2014; 11: 609-623.
 324 Anderson J, Chris GVdW. Fundamentals of zinc oxide as a semiconductor. *Reports on Progress in Physics*
 325 2009; 72: 126501.
 326 Andriotis AN, Menon M. Band gap engineering via doping: A predictive approach. *Journal of Applied*
 327 *Physics* 2015; 117: 125708.
 328 Ansari SA, Khan MM, Ansari MO, Kalathil S, Lee J, Cho MH. Band gap engineering of CeO₂ nanostructure
 329 using an electrochemically active biofilm for visible light applications. *RSC Advances* 2014; 4:
 330 16782-16791.
 331 Asthana A, Momeni K, Prasad A, Yap YK, Yassar RS. On the correlation of crystal defects and band gap
 332 properties of ZnO nanobelts. *Applied Physics A* 2011; 105: 909-914.
 333 Bar-Ilan O, Louis KM, Yang SP, Pedersen JA, Hamers RJ, Peterson RE, et al. Titanium dioxide nanoparticles
 334 produce phototoxicity in the developing zebrafish. *Nanotoxicology* 2012; 6: 670-679.
 335 Bharati P, Aslam M, Bahadur D. Effect of Fe doping concentration on optical and magnetic properties of
 336 ZnO nanorods. *Nanotechnology* 2012; 23: 115601.
 337 Bhat SV, Deepak F. Tuning the bandgap of ZnO by substitution with Mn²⁺, Co²⁺ and Ni²⁺. *Solid State*
 338 *Communications* 2005; 135: 345-347.
 339 Brown GE, Parks GA. Sorption of Trace Elements on Mineral Surfaces: Modern Perspectives from
 340 Spectroscopic Studies, and Comments on Sorption in the Marine Environment. *International*
 341 *Geology Review* 2001; 43: 963-1073.
 342 Brun NR, Christen V, Furrer G, Fent K. Indium and indium tin oxide induce endoplasmic reticulum stress
 343 and oxidative stress in Zebrafish (*Danio rerio*). *Environmental Science & Technology* 2014; 48:
 344 11679-11687.
 345 Brunet L, Lyon DY, Hotze EM, Alvarez PJJ, Wiesner MR. Comparative Photoactivity and Antibacterial
 346 Properties of C60 Fullerenes and Titanium Dioxide Nanoparticles. *Environmental Science &*
 347 *Technology* 2009; 43: 4355-4360.
 348 Buerki-Thurnherr T, Xiao L, Diener L, Arslan O, Hirsch C, Maeder-Althaus X, et al. In vitro mechanistic
 349 study towards a better understanding of ZnO nanoparticle toxicity. *Nanotoxicology* 2013; 7: 402-
 350 416.
 351 Buonsanti R, Milliron DJ. Chemistry of doped colloidal nanocrystals. *Chemistry of Materials* 2013; 25:
 352 1305-1317.
 353 Burello E, Worth AP. A theoretical framework for predicting the oxidative stress potential of oxide
 354 nanoparticles. *Nanotoxicology* 2011; 5: 228-235.
 355 Chairuangkitti P, Lawanprasert S, Roytrakul S, Aueviriyavit S, Phummiratch D, Kulthong K, et al. Silver
 356 nanoparticles induce toxicity in A549 cells via ROS-dependent and ROS-independent pathways.
 357 *Toxicology in Vitro* 2013; 27: 330-338.
 358 Chambers BA, Afrooz ARMN, Bae S, Aich N, Katz L, Saleh NB, et al. Effects of chloride and ionic strength
 359 on physical morphology, dissolution, and bacterial toxicity of silver nanoparticles. *Environmental*
 360 *Science & Technology* 2014; 48: 761-769.
 361 Chen S-Y, Chen R-J, Lee W, Dong C-L, Gloter A. Spectromicroscopic evidence of interstitial and
 362 substitutional dopants in association with oxygen vacancies in Sm-doped ceria nanoparticles.
 363 *Physical Chemistry Chemical Physics* 2014; 16: 3274-3281.
 364 Chen W, Zhang JZ, Joly AG. Optical properties and potential applications of doped semiconductor
 365 nanoparticles. *Journal of nanoscience and nanotechnology* 2004; 4: 919-947.
 366 Chen X, Liu L, Yu PY, Mao SS. Increasing solar absorption for photocatalysis with black hydrogenated
 367 titanium dioxide nanocrystals. *Science* 2011; 331: 746-750.
 368 Chusuei CC, Wu C-H, Mallavarapu S, Hou FYS, Hsu C-M, Winiarz JG, et al. Cytotoxicity in the age of nano:
 369 The role of fourth period transition metal oxide nanoparticle physicochemical properties.
 370 *Chemico-Biological Interactions* 2013; 206: 319-326.

371 Das PP, Agarkar SA, Mukhopadhyay S, Manju U, Ogale SB, Devi PS. Defects in chemically synthesized and
 372 thermally processed ZnO nanorods: Implications for active layer properties in dye-sensitized solar
 373 cells. *Inorganic Chemistry* 2014; 53: 3961-3972.
 374 Devan RS, Patil RA, Lin J-H, Ma Y-R. One-Dimensional Metal-Oxide Nanostructures: Recent Developments
 375 in Synthesis, Characterization, and Applications. *Advanced Functional Materials* 2012; 22: 3326-
 376 3370.
 377 Djurisić AB, Leung YH, Ching Ng AM. Strategies for improving the efficiency of semiconductor metal oxide
 378 photocatalysis. *Materials Horizons* 2014; 1: 400-410.
 379 Djurišić AB, Leung YH, Ng AMC, Xu XY, Lee PKH, Degger N, et al. Toxicity of metal oxide nanoparticles:
 380 Mechanisms, characterization, and avoiding experimental artefacts. *Small* 2015; 11: 26-44.
 381 Faisal M, Ismail AA, Ibrahim AA, Bouzid H, Al-Sayari SA. Highly efficient photocatalyst based on Ce doped
 382 ZnO nanorods: Controllable synthesis and enhanced photocatalytic activity. *Chemical Engineering*
 383 *Journal* 2013; 229: 225-233.
 384 Fecht HJ. Nanostructure formation by mechanical attrition. *Nanostructured Materials* 1995; 6: 33-42.
 385 Gajewicz A, Schaeublin N, Rasulev B, Hussain S, Leszczynska D, Puzyn T, et al. Towards understanding
 386 mechanisms governing cytotoxicity of metal oxides nanoparticles: Hints from nano-QSAR studies.
 387 *Nanotoxicology* 2015; 0: 1-13.
 388 Garcia G, Buonsanti R, Runnerstrom EL, Mendelsberg RJ, Llodes A, Anders A, et al. Dynamically
 389 modulating the surface plasmon resonance of doped semiconductor nanocrystals. *Nano Letters*
 390 2011; 11: 4415-4420.
 391 George S, Lin S, Ji Z, Thomas CR, Li L, Mecklenburg M, et al. Surface defects on plate-shaped silver
 392 nanoparticles contribute to its hazard potential in a fish gill cell line and Zebrafish embryos. *ACS*
 393 *Nano* 2012; 6: 3745-3759.
 394 Gilstrap RAJ. A colloidal nanoparticle form of indium tin oxide: System development and characterization.
 395 *Material Science and Engineering*. PhD. Georgia Institute of Technology, Atlanta, GA, 2009.
 396 Goings JJ, Schimpf AM, May JW, Johns RW, Gamelin DR, Li X. Theoretical Characterization of Conduction-
 397 Band Electrons in Photodoped and Aluminum-Doped Zinc Oxide (AZO) Quantum Dots. *The*
 398 *Journal of Physical Chemistry C* 2014; 118: 26584-26590.
 399 Guo MY, Ng AMC, Liu F, Djurišić AB, Chan WK, Su H, et al. Effect of native defects on photocatalytic
 400 properties of ZnO. *The Journal of Physical Chemistry C* 2011; 115: 11095-11101.
 401 Guo Y, Zhang X-w, Weng W-H, Han G-r. Structure and properties of nitrogen-doped titanium dioxide thin
 402 films grown by atmospheric pressure chemical vapor deposition. *Thin Solid Films* 2007; 515:
 403 7117-7121.
 404 Hoque A, Boruah R, Das SK. Tunable optical properties of ZnO via doping monovalent (Li^+), divalent (Mn^{2+})
 405 and trivalent (Fe^{3+}) cations. *Materials Chemistry and Physics* 2014; 147: 213-217.
 406 Ischenko V, Polarz S, Grote D, Stavarache V, Fink K, Driess M. Zinc Oxide Nanoparticles with Defects.
 407 *Advanced Functional Materials* 2005; 15: 1945-1954.
 408 Janotti A, Van de Walle CG. New insights into the role of native point defects in ZnO. *Journal of Crystal*
 409 *Growth* 2006; 287: 58-65.
 410 Janotti A, Van de Walle CG. Native point defects in ZnO. *Physical Review B* 2007; 76: 165202.
 411 Jitti-a-Porn P, Suwanhoon S, Amornpitoksuk P, Patarapaiboolchai O. Defects and the optical band gap of
 412 ZnO nanoparticles prepared by a grinding method. *Journal of Ceramic Processing Research* 2011;
 413 12: 85-89.
 414 Ju-Nam Y, Lead JR. Manufactured nanoparticles: An overview of their chemistry, interactions and
 415 potential environmental implications. *Science of The Total Environment* 2008; 400: 396-414.
 416 Kaweeteerawat C, Ivask A, Liu R, Zhang H, Chang CH, Low-Kam C, et al. Toxicity of metal oxide
 417 nanoparticles in *Escherichia coli* correlates with conduction band and hydration energies.
 418 *Environmental Science & Technology* 2015; 49: 1105-1112.

419 Khan MM, Ansari SA, Pradhan D, Ansari MO, Han DH, Lee J, et al. Band gap engineered TiO₂ nanoparticles
 420 for visible light induced photoelectrochemical and photocatalytic studies. *Journal of Materials*
 421 *Chemistry A* 2014a; 2: 637-644.

422 Khan MM, Ansari SA, Pradhan D, Han DH, Lee J, Cho MH. Defect-induced band gap narrowed CeO₂
 423 nanostructures for visible light activities. *Industrial & Engineering Chemistry Research* 2014b; 53:
 424 9754-9763.

425 Klaine SJ, Alvarez PJJ, Batley GE, Fernandes TF, Handy RD, Lyon DY, et al. Nanomaterials in the
 426 environment: Behavior, fate, bioavailability, and effects. *Environmental Toxicology & Chemistry*
 427 2008; 27: 1825-1851.

428 Kumar A, Pandey AK, Singh SS, Shanker R, Dhawan A. Engineered ZnO and TiO₂ nanoparticles induce
 429 oxidative stress and DNA damage leading to reduced viability of *Escherichia coli*. *Free Radical*
 430 *Biology and Medicine* 2011; 51: 1872-1881.

431 Kumar SG, Rao KSRK. Zinc oxide based photocatalysis: tailoring surface-bulk structure and related
 432 interfacial charge carrier dynamics for better environmental applications. *RSC Advances* 2015; 5:
 433 3306-3351.

434 Laks D, Van de Walle C, Neumark G, Pantelides S. Role of native defects in wide-band-gap
 435 semiconductors. *Physical review letters* 1991; 66: 648.

436 Lakshmi Prasanna V, Vijayaraghavan R. Insight into the Mechanism of Antibacterial Activity of ZnO:
 437 Surface Defects Mediated Reactive Oxygen Species Even in the Dark. *Langmuir* 2015; 31: 9155-
 438 9162.

439 Lawrence NJ, Brewer JR, Wang L, Wu T-S, Wells-Kingsbury J, Ihrig MM, et al. Defect engineering in cubic
 440 cerium oxide nanostructures for catalytic oxidation. *Nano Letters* 2011; 11: 2666-2671.

441 Leach AM, McDowell M, Gall K. Deformation of Top-Down and Bottom-Up Silver Nanowires. *Advanced*
 442 *Functional Materials* 2007; 17: 43-53.

443 Li Y, Niu J, Zhang W, Zhang L, Shang E. Influence of aqueous media on the ROS-mediated toxicity of ZnO
 444 nanoparticles toward green fluorescent protein-expressing *Escherichia coli* under UV-365
 445 irradiation. *Langmuir* 2014; 30: 2852-2862.

446 Li Y, Zhang W, Niu J, Chen Y. Mechanism of Photogenerated Reactive Oxygen Species and Correlation
 447 with the Antibacterial Properties of Engineered Metal-Oxide Nanoparticles. *ACS Nano* 2012; 6:
 448 5164-5173.

449 Lison D, Laloy J, Corazzari I, Muller J, Rabolli V, Panin N, et al. Sintered indium-tin-oxide (ITO) particles: A
 450 new pneumotoxic entity. *Toxicological Sciences* 2009; 108: 472-481.

451 Liu X, Wu X, Cao H, Chang RPH. Growth mechanism and properties of ZnO nanorods synthesized by
 452 plasma-enhanced chemical vapor deposition. *Journal of Applied Physics* 2004; 95: 3141-3147.

453 Lounis SD, Runnerstrom EL, Bergerud A, Nordlund D, Milliron DJ. Influence of Dopant Distribution on the
 454 Plasmonic Properties of Indium Tin Oxide Nanocrystals. *Journal of the American Chemical Society*
 455 2014a; 136: 7110-7116.

456 Lounis SD, Runnerstrom EL, Llordés A, Milliron DJ. Defect chemistry and plasmon physics of colloidal
 457 metal oxide nanocrystals. *The Journal of Physical Chemistry Letters* 2014b; 5: 1564-1574.

458 McCluskey MD, Jokela SJ. Defects in ZnO. *Journal of Applied Physics* 2009; 106: 1-13.

459 Merz TA, Doult DR, Bolton T, Dong Y, Brillson LJ. Nanostructure growth-induced defect formation and
 460 band bending at ZnO surfaces. *Surface Science* 2011; 605: L20-L23.

461 Murphy CJ, Sau TK, Gole AM, Orendorff CJ, Gao J, Gou L, et al. Anisotropic metal nanoparticles: synthesis,
 462 assembly, and optical applications. *The Journal of Physical Chemistry B* 2005; 109: 13857-13870.

463 Myneni SCB, Brown JT, Martinez GA, Meyer-Ilse W. Imaging of Humic Substance Macromolecular
 464 Structures in Water and Soils. *Science* 1999; 286: 1335-1337.

465 Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. *Science* 2006; 311: 622-627.

466 Norris DJ, Efros AL, Erwin SC. Doped nanocrystals. *Science* 2008; 319: 1776-1779.

- Otero-González L, García-Saucedo C, Field JA, Sierra-Álvarez R. Toxicity of TiO_2 , ZrO_2 , Fe^0 , Fe_2O_3 , and Mn_2O_3 nanoparticles to the yeast, *Saccharomyces cerevisiae*. Chemosphere 2013; 93: 1201-1206.
- Pacurari M, Qian Y, Fu W, Schwegler-Berry D, Ding M, Castranova V, et al. Cell permeability, migration, and reactive oxygen species induced by multiwalled carbon nanotubes in human microvascular endothelial cells. Journal of Toxicology and Environmental Health, Part A 2011; 75: 112-128.
- Pan X, Yang M-Q, Fu X, Zhang N, Xu Y-J. Defective TiO_2 with oxygen vacancies: synthesis, properties and photocatalytic applications. Nanoscale 2013; 5: 3601-3614.
- Park E-J, Choi J, Park Y-K, Park K. Oxidative stress induced by cerium oxide nanoparticles in cultured BEAS-2B cells. Toxicology 2008; 245: 90-100.
- Pelaez M, Nolan NT, Pillai SC, Seery MK, Falaras P, Kontos AG, et al. A review on the visible light active titanium dioxide photocatalysts for environmental applications. Applied Catalysis B: Environmental 2012; 125: 331-349.
- Polarz S, Roy A, Merz M, Halm S, Schröder D, Schneider L, et al. Chemical Vapor Synthesis of Size-Selected Zinc Oxide Nanoparticles. Small 2005; 1: 540-552.
- Rehman S, Ullah R, Butt AM, Gohar ND. Strategies of making TiO_2 and ZnO visible light active. Journal of Hazardous Materials 2009; 170: 560-569.
- Röhder LA, Brandt T, Sigg L, Behra R. Influence of agglomeration of cerium oxide nanoparticles and speciation of cerium(III) on short term effects to the green algae *Chlamydomonas reinhardtii*. Aquatic Toxicology 2014; 152: 121-130.
- Rossi T, Penfold TJ, Rittmann-Frank MH, Reinhard M, Rittmann J, Borca CN, et al. Characterizing the Structure and Defect Concentration of ZnO Nanoparticles in a Colloidal Solution. The Journal of Physical Chemistry C 2014; 118: 19422-19430.
- Saleh NB, Afrooz A, Bisesi Jr JH, Aich N, Plazas-Tuttle J, Sabo-Attwood T. Emergent properties and toxicological considerations for nanohybrid materials in aquatic systems. Nanomaterials 2014; 4: 372-407.
- Saleh NB, Aich N, Lead J, Plazas-Tuttle J, Lowry GV. Research strategy to determine when novel nanohybrids pose unique environmental risks. Environmental Science: Nano 2015; 2: 11-18 (Cover Article).
- Sarkar A, Ghosh M, Sil PC. Nanotoxicity: Oxidative stress mediated toxicity of metal and metal oxide nanoparticles. Journal of Nanoscience and Nanotechnology 2014; 14: 730-743.
- Sauer G, Brehm G, Schneider S, Nielsch K, Wehrspohn RB, Choi J, et al. Highly ordered monocrystalline silver nanowire arrays. Journal of Applied Physics 2002; 91: 3243.
- Schimpf AM, Lounis SD, Runnerstrom EL, Milliron DJ, Gamelin DR. Redox Chemistries and Plasmon Energies of Photodoped In_2O_3 and Sn-Doped In_2O_3 (ITO) Nanocrystals. J. Am. Chem. Soc. (Accepted) 2014a.
- Schimpf AM, Lounis SD, Runnerstrom EL, Milliron DJ, Gamelin DR. Redox Chemistries and Plasmon Energies of Photodoped In_2O_3 and Sn-Doped In_2O_3 (ITO) Nanocrystals. Journal of the American Chemical Society 2014b.
- Schimpf AM, Ochsenbein ST, Buonsanti R, Milliron DJ, Gamelin DR. Comparison of Extra Electrons in Colloidal n-Type Al^{3+} -Doped and Photochemically Reduced ZnO Nanocrystals. Chemical Communications 2012.
- Schmidt-Mende L, MacManus-Driscoll JL. ZnO – nanostructures, defects, and devices. Materials Today 2007; 10: 40-48.
- Sekiguchi T, Miyashita S, Obara K, Shishido T, Sakagami N. Hydrothermal growth of ZnO single crystals and their optical characterization. Journal of Crystal Growth 2000; 214–215: 72-76.
- Sharma V, Anderson D, Dhawan A. Zinc oxide nanoparticles induce oxidative DNA damage and ROS-triggered mitochondria mediated apoptosis in human liver cells (HepG2). Apoptosis 2012; 17: 852-870.

- Song W, Zhang J, Guo J, Zhang J, Ding F, Li L, et al. Role of the dissolved zinc ion and reactive oxygen species in cytotoxicity of ZnO nanoparticles. *Toxicology Letters* 2010; 199: 389-397.
- Tam KH, Cheung CK, Leung YH, Djurišić AB, Ling CC, Beling CD, et al. Defects in ZnO Nanorods Prepared by a Hydrothermal Method. *The Journal of Physical Chemistry B* 2006; 110: 20865-20871.
- von Moos N, Slaveykova VI. Oxidative stress induced by inorganic nanoparticles in bacteria and aquatic microalgae – state of the art and knowledge gaps. *Nanotoxicology* 2014; 8: 605-630.
- Wang H, Jia L, Bogdanoff P, Fiechter S, Mohwald H, Shchukin D. Size-related native defect engineering in high intensity ultrasonication of nanoparticles for photoelectrochemical water splitting. *Energy & Environmental Science* 2013; 6: 799-804.
- Wang J, Wang Z, Huang B, Ma Y, Liu Y, Qin X, et al. Oxygen vacancy induced band-gap narrowing and enhanced visible light photocatalytic activity of ZnO. *ACS Applied Materials & Interfaces* 2012a; 4: 4024-4030.
- Wang N, Cai Y, Zhang RQ. Growth of nanowires. *Materials Science and Engineering: R: Reports* 2008; 60: 1-51.
- Wang Z, Li N, Zhao J, White JC, Qu P, Xing B. CuO nanoparticle interaction with human epithelial cells: Cellular uptake, location, export, and genotoxicity. *Chemical Research in Toxicology* 2012b; 25: 1512-1521.
- Wang Z, Zu X, Zhu S, Wang L. Green luminescence originates from surface defects in ZnO nanoparticles. *Physica E: Low-dimensional Systems and Nanostructures* 2006; 35: 199-202.
- Ward MR, Boyes ED, Gai PL. Aberration Corrected (S)TEM and Nano Beam Diffraction (NBD) of Pt and Pd on Al₂O₃ Catalysts. *Journal of Physics: Conference Series* 2014; 522: 012068.
- Warwick T, Franck K, Kortright J, Meigs G, Moronne M, Myneni S, et al. A scanning transmission x-ray microscope for materials science spectromicroscopy at the advanced light source. *Review of scientific instruments* 1998; 69: 2964-2973.
- Waychunas GA, Zhang H. Structure, Chemistry, and Properties of Mineral Nanoparticles. *Elements* 2008; 4: 381-387.
- Xing YJ, Xi ZH, Xue ZQ, Zhang XD, Song JH, Wang RM, et al. Optical properties of the ZnO nanotubes synthesized via vapor phase growth. *Applied Physics Letters* 2003; 83: 1689.
- Xue X-D, Wang T, Jiang J, Wu Y-C. Hydrogen- and corrosion-induced defect characterization of ZnO single crystal: A slow positron beam study. *physica status solidi (a)* 2013; 210: 1418-1423.
- Yang X, Gondikas AP, Marinakos SM, Auffan M, Liu J, Hsu-Kim H, et al. Mechanism of silver nanoparticle toxicity is dependent on dissolved silver and surface coating in *Caenorhabditis elegans*. *Environmental Science & Technology* 2011; 46: 1119-1127.
- Yin H, Casey PS. Effects of iron or manganese doping of ZnO nanoparticles on their dissolution, ROS generation and cytotoxicity. *RSC Advances* 2014; 4: 26149-26157.
- Zhang C, Lin J. Defect-related luminescent materials: synthesis, emission properties and applications. *Chemical Society Reviews* 2012; 41: 7938-7961.
- Zhang H, Ji Z, Xia T, Meng H, Low-Kam C, Liu R, et al. Use of metal oxide nanoparticle band gap to develop a predictive paradigm for oxidative stress and acute pulmonary inflammation. *ACS Nano* 2012; 6: 4349-4368.
- Zhang L, Jiang Y, Ding Y, Daskalakis N, Jeuken L, Povey M, et al. Mechanistic investigation into antibacterial behaviour of suspensions of ZnO nanoparticles against *E. coli*. *Journal of Nanoparticle Research* 2010; 12: 1625-1636.
- Zhang X, Qin J, Xue Y, Yu P, Zhang B, Wang L, et al. Effect of aspect ratio and surface defects on the photocatalytic activity of ZnO nanorods. *Sci. Rep.* 2014; 4.
- Zhang Z, Fenter P, Cheng L, Sturchio NC, Bedzyk MJ, Předota M, et al. Ion Adsorption at the Rutile–Water Interface: Linking Molecular and Macroscopic Properties. *Langmuir* 2004; 20: 4954-4969.

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Table 1. Conflicting toxicity mechanisms of reported for metal oxide nanoparticles.

Particle	ROS Mediation	Non-ROS Mediation
Ag	<p><i>Key mechanism:</i> ROS resulted in apoptosis to eukaryotic cells.</p> <p><i>Particle sources:</i> Sigma Aldrich using polyol reduction of silver salts (Catalog # 576832, St. Louis, MO, USA) (Chairuangkitti et al., 2013) and Air Force Research Laboratory (Brooks AFB, TX, USA) (Hussain et al., 2005).</p>	<p><i>Key Mechanism:</i> Dissolution</p> <p><i>Particle sources:</i> In-house synthesis with mercaptosuccinic acid capping by sodium borohydrate mediated reduction of silver nitrate (Chambers et al., 2014), citrate (by sodium citrate mediated reduction of sodium nitrate) and gum Arabic coatings (by sodium borohydrate mediated reduction of silver</p>

		nitrate) (Yang et al., 2011); NanoAmor (Houston, TX, USA) commercial source with polyvinyl pyrrolidone (PVP) coating (Yang et al., 2011).
ZnO	<p><i>Key mechanism:</i> ROS-mediated bacterial inactivation and cytotoxicity.</p> <p><i>Particle sources:</i> In-house synthesis by flame spray pyrolysis (Kaweeteerawat et al., 2015); Sigma Chemical Co. Ltd or Sigma Aldrich Co. LLC (Kumar et al., 2011; Li et al., 2014; Sharma et al., 2012).</p>	<p><i>Key mechanism:</i> Dissolved ion toxicity to bacteria, zebrafish, and human cells.</p> <p><i>Particle sources:</i> In-house synthesis by flame spray pyrolysis (Zhang et al., 2012); IBU-tec Advanced Materials AG (Weimar, Germany) (Buerki-Thurnherr et al., 2013); Nanostructured and Amorphous Materials, (Los Alamos, NM, USA) (Chusei et al., 2013).</p>
CuO	<p><i>Key mechanism:</i> ROS-mediated toxicity to bacteria and human cell lines.</p> <p><i>Particle sources:</i> In-house synthesis by flame spray pyrolysis (Kaweeteerawat et al., 2015); Beijing Nanchen S&T Ltd., Beijing, China (Wang et al., 2012b).</p>	<p><i>Key mechanism:</i> Dissolution-mediated cytotoxicity to human cell lines.</p> <p><i>Particle sources:</i> In-house synthesis by flame spray pyrolysis (Zhang et al., 2012); Nanostructured and Amorphous Materials (Los Alamos, NM, USA) (Chusuei et al., 2013).</p>
CeO ₂	<p><i>Key mechanism:</i> Cytotoxicity to human bronchial epithelial cells (BEAS-2B) from ROS.</p> <p><i>Particle source:</i> In-house supercritical synthesis (Park et al., 2008).</p>	<p><i>Key mechanism:</i> Dissolution based toxicity to aquatic organism.</p> <p><i>Particle source:</i> Commercial Nanograde, Staefa, Switzerland (Röhder et al., 2014).</p>
Mn ₂ O ₃	<p><i>Key mechanism:</i> ROS-mediated toxicity to bacteria, yeast, and human cell lines.</p> <p><i>Particle sources:</i> In-house synthesis by flame spray pyrolysis (Kaweeteerawat et al., 2015; Zhang et al., 2012); Sky-Spring Nanomaterials, (Houston, TX, USA (Otero-González et al., 2013).</p>	<p><i>Key mechanism:</i> Dissolution-mediated cytotoxicity.</p> <p><i>Particle source:</i> Nanostructured and Amorphous Materials (Los Alamos, NM, USA) (Chusuei et al., 2013).</p>

Fig. 1. (a) un-doped ZnO nanoparticle and its band structure showing electrical conduction band (E_c) distant from cellular redox potential (CRP). (b) ROS active doped-ZnO nanoparticle and its E_c re-positioning within CRP via doping-induced band bending.

Fig. 2. Distribution of (a) dopant ions and (b) defects or vacancies in a crystal structure.