Toxic effects of metal oxide nanoparticles and their underlying mechanisms

Yanli Wang^{1,2}, Lin Ding¹, Chenjie Yao¹, Chenchen Li¹, Xiaojun Xing¹, Yanan Huang¹, Tianjiao Gu¹ and Minghong Wu^{1*}

ABSTRACT Nanomaterials have attracted considerable interest owing to their unique physicochemical properties. The wide application of nanomaterials has raised many concerns about their potential risks to human health and the environment. Metal oxide nanoparticles (MONPs), one of the main members of nanomaterials, have been applied in various fields, such as food, medicine, cosmetics, and sensors. This review highlights the bio-toxic effects of widely applied MONPs and their underlying mechanisms. Two main underlying toxicity mechanisms, reactive oxygen species (ROS)- and non-ROS-mediated toxicities, of MONPs have been widely accepted. ROS activates oxidative stress, which leads to lipid peroxidation and cell membrane damage. In addition, ROS can trigger the apoptotic pathway by activating caspase-9 and -3. Non-ROS-mediated toxicity mechanism includes the effect of released ions, excessive accumulation of NPs on the cell surface, and combination of NPs with specific death receptors. Furthermore, the combined toxicity evaluation of some MONPs is also discussed. Toxicity may dramatically change when nanomaterials are used in a combined system because the characteristics of NPs that play a key role in their toxicity such as size, surface properties, and chemical nature in the complex system are different from the pristine NPs.

Keywords: metal oxide nanoparticles, bio-toxicity effect, nanotoxicology, underlying mechanism

INTRODUCTION

Over the past few decades, nanotechnology has been considered as one of the most potential technologies [1]. With the rapid development of nanotechnology, metal oxide nanoparticles (MONPs) have been widely used in various fields, such as electronic devices, cosmetics, paints, additives in food, and biological and medical systems

[2–6]. However, their potential risks to human health and the environment have attracted the attention of scientists worldwide. Recently, many studies have suggested that MONPs exert adverse effects on various organs leading to serious health problems [7–11]. Therefore, study on the biological safety of these NPs is a very essential and blossoming field, which mainly focuses on investigating the potential adverse effects of NPs and their potential toxicity mechanisms [12–15]. Systematical study on the bio-effects of MONPs and their mechanisms not only protects human health and the environment, but also contributes to maximizing the application of nanomaterials in various fields safely.

In this review, we discuss the bio-toxicity of several commonly used MONPs (titanium oxide (TiO₂) NPs, zinc oxide (ZnO) NPs, and iron oxide (IO) NPs), and highlight the toxicological mechanisms of these NPs. Studies on the toxic effects of these NPs focus on both *in vitro* and *in vivo* investigations. MONPs can easily pass through the cell membrane and directly induce cell death *in vitro*. Furthermore, MONPs cause damage to the organs after entering the body *in vivo*. Currently, the toxicity mechanism is mainly divided into reactive oxygen species (ROS)- and non-ROS-mediated toxicities. ROS-mediated toxicity is one of the most recognized toxicity mechanisms of MONPs. ROS activates oxidative stress, which results in cell membrane damage, protein denaturation, DNA damage, and mitochondrial membrane permeability change. Besides, ROS can activate caspase-9 and -3, and trigger the apoptotic pathway. In addition, researchers have also discovered several non-ROS-related mechanisms including the effect of released ions, excessive accumulation of

¹ Institute of Nano-chemistry and Nano-biology, Shanghai University, Shanghai 200444, China

² Harvard School of Public Health, Harvard University, Boston, Massachusetts, 02115, USA

* Corresponding author (email: mhwu@shu.edu.cn)

NPs on the cell surface, and combination of NPs with specific death receptors. Furthermore, we summarize combined toxicity and its influence when MONPs are mixed in complex systems. Once the NPs combine with other substances, their physicochemical characteristics such as size, surface properties, and chemical nature would change, influencing their potential toxicity. However, previous studies are mostly limited to single NPs in comprehending the risk of NPs. Hence, we should pay more attention to the effect of combined toxicity. This review is aimed at improving the performance of MONP application in various fields and reducing their potential hazard.

TOXIC EFFECTS OF MONPs

MONPs display potential utility in many applications, including food, cosmetics, nanomedicines, solar cells, and catalytic agents. Among these MONPs, TiO_2 , ZnO, and IO NPs have received the most attention owing to their wide application and unique physical and chemical properties [16–18]. Large-scale manufacturing and consumer utilization of MONPs pose increasing risks to human health and the environment. Thus, systematic bio-safety study of MONPs is highly warranted, including the bio-effects in biological systems and mechanism of toxicology.

Titanium dioxide nanoparticles

TiO_2 , a white odorless crystalline powder, is deemed a low or even non-toxic material [19–21]. TiO_2 NPs are manufactured worldwide and commonly used in many fields, such as paints, cosmetics, photosensitive materials, and food additives [22,23]. With the development of nanomedicine, the application of TiO_2 NPs in biomedicine as carriers in drug and gene delivery has become very common [24,25]. According to the National Nanotechnology Initiative of America, TiO_2 NPs are the most widely produced NPs in the world [24]. With large-scale manufacturing and utilization, humans are facing more exposure to TiO_2 NPs, resulting in toxic interactions. Therefore, the potential hazards of TiO_2 NPs on human health attract people's concern. There have been many studies on the bio-toxicity of TiO_2 NPs [26].

In vitro studies

Some studies showed that the toxicity of TiO_2 NPs is relatively low [24,27]. Pujalte *et al.* [27] reported that compared with the toxicity of ZnO and CdS NPs in IP15 (glomerular mesangial) and HK-2 (proximal tubule epithelial) cell lines, TiO_2 NPs showed no obvious cell damage even at higher concentrations ($> 20 \mu\text{g cm}^{-2}$). The

IC_{50} (defined as concentration which induces 50% cell mortality) values for ZnO and CdS were 3.04 ± 0.07 and $4.85 \pm 0.06 \mu\text{g cm}^{-2}$, respectively. Only slight toxicity was observed for TiO_2 NPs at concentrations of 80 and $160 \mu\text{g cm}^{-2}$. However, other studies showed that TiO_2 NPs exhibited significant cytotoxicity [22,28]. Butler *et al.* [29] reported that TiO_2 NPs were endocytosed by *Salmonella typhimurium*, which caused mutagenicity in TA98 and TA1537 strains. Valdiglesias *et al.* [30] studied the cytotoxic and genotoxic potential of TiO_2 NPs. They indicated that TiO_2 NPs induced the reduction of mitochondrial dehydrogenase activity and mitochondrial membrane potential in human lymphocytes, leading to cell apoptosis. Wang *et al.* [31] pointed out that microtubules was destroyed after treatment of 4T1 cells with 50 and 200 mg L^{-1} of TiO_2 NPs (Fig. 1a–h).

Many factors, such as size, shape, surface chemical property, dispersion, dosage, and time have effects on toxicity evaluation of NPs [32–34]. Zhang *et al.* [35] studied the toxicity of 5 and 32 nm TiO_2 NPs in murine MC3T3-E1 preosteoblasts. The results showed that cells treated with 5 nm TiO_2 NPs stimulated lactate dehydrogenase (LDH) release, mitochondrial damage, and apoptosis more significantly compared with those treated with 32 nm TiO_2 NPs. In addition, size-dependent cytotoxicity effect was observed in RAW264.7 (murine macrophage) and BEAS-2B (human bronchial epithelial) cells after 2 h incubation with different sizes of TiO_2 NPs [36]. These results indicate that the toxicity of TiO_2 NPs is size-dependent. Several other studies showed that testing conditions, such as dispersion of NPs, might have a great impact on cytotoxicity. Magdolenova *et al.* [24] compared two kinds of TiO_2 NPs with different stabilities and agglomeration states. They demonstrated that the dispersion possessing better stability showed severe cytotoxicity compared with the dispersion with agglomeration. Besides, Thomas *et al.* [25] also obtained a similar result.

Interactions between the cells and NPs, including cellular uptake, subcellular localization, and metabolism present the most primitive fundamental phenomenon, which are very important for the study of NPs toxicity. Wang *et al.* [37] studied the sub-cellular location of TiO_2 nanotubes (TiO_2 -NTs) in neural stem cells. It is reported that TiO_2 -NTs can be internalized into the cells after 24 h of incubation. Furthermore, they also found that TiO_2 -NTs passed through the nuclear pore complex entering the cell nucleus after 48 h of co-incubation [38]. Besides, they also investigated endocytosis, exocytosis, and the related mechanisms [39]. It is indicated that both endocytosis and exocytosis

Figure 1 (a–h) Microtubule dynamics following exposure to TiO_2 NPs using immunofluorescence staining: (a–d) fluorescence images of 4T1 cells examined under a laser scanning confocal microscope and (e–h) phase contrast images of 4T1 cells. (a, e) Control group (treated in the absence of TiO_2 NPs); (b, f) groups treated with 200 mg L^{-1} TiO_2 NPs for 24 h; (c, g) 50 mg L^{-1} TiO_2 NPs for 48 h, and (d, h) 200 mg L^{-1} TiO_2 NPs for 48 h. (i–p) Representative histological photomicrographs of the liver in young and adult rats after gastrointestinal exposure to TiO_2 NPs for 30 days. Circles: liver edema in young rats. Arrows: inflammatory cell infiltration in adult rat liver Y0–Y3: young rats, A0–A3: adult rats, Y0 & A0: control group (0 mg kg^{-1}), Y1 & A1: low-dose exposure group (10 mg kg^{-1}), Y2 & A2: middle-dose exposure group (50 mg kg^{-1}), Y3 & A3: high-dose exposure group (200 mg kg^{-1}). Reprinted with permission from: (a–h) Ref. [31], Copyright 2015, Royal Society of Chemistry; (i–p) Ref. [49], Copyright 2013, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

of TiO_2 NPs are energy-dependent. NPs enter into the cells via a receptor-mediated pathway. The endocytosis rate of TiO_2 NPs was highly dependent on size and shape, while the exocytosis ratio was largely dependent on the original concentration, endocytosis amount and shapes, but was less affected by size.

In vivo studies

Compared with *in vitro* studies, *in vivo* studies can provide data in abundance. Many researchers studied the *in vivo* toxicity of TiO_2 NPs. TiO_2 NPs can enter into the human body via various routes [40], increasing their potential hazard to human health. The skin is the largest organ in our body that is exposed to nanomaterials. Lademann *et al.* [41] reported that TiO_2 NPs can pass through the human stratum corneum and reach the epidermis, and even the dermis. In addition, Wu *et al.* [42] showed that TiO_2 NPs penetrate through the skin, and reach major organs in mice. Another possible entry route of TiO_2 NPs is via res-

piratory tract. Many studies demonstrated that NPs reach the highly vascularized alveoli regions in deep lung [43,44]. Some studies reported the pulmonary toxicity of TiO_2 NP exposure in terms of increased bronchoalveolar lavage inflammatory parameters [45–47]. In addition, TiO_2 NPs enter into the human body through food directly. Chen *et al.* [48] studied TiO_2 NPs in sugar-coated gum. They showed that TiO_2 NPs passed through the gastrointestinal tract and distributed to other organs, resulting in their gradual accumulation in the whole body. Wang *et al.* [49] studied the oral toxicity of TiO_2 NPs in young and adult rats. Pathological and histological analysis revealed that treatment with high-dose TiO_2 NPs (200 mg kg^{-1}) induced liver edema, hepatic cord disarray, perilobular cell swelling, hydropic degeneration, or vacuolization in young rats. Inflammatory cell infiltration was observed in adult rat liver (10 and 50 mg kg^{-1} TiO_2 NP-treated groups; Fig. 1i–p). Biochemical parameters in the serum (Table 1) showed that decrease in total bilirubin (TBIL) and increase in blood urea nitrogen

Table 1 Biochemistry assay of serum in rats after gastrointestinal exposure to TiO₂ NPs for 30 days (mean ± SD, *n* = 7) [49]

Group	Exposure dose	Glu [mmol L ⁻¹]	TCHO [mmol L ⁻¹]	TG [mmol L ⁻¹]	HDL-C [mmol L ⁻¹]	LDL-C [mmol L ⁻¹]	TP [g L ⁻¹]	ALB [g L ⁻¹]	GLB [g L ⁻¹]	ALB/GLB
Youth										
Y0	0 mg kg ⁻¹ BW	5.04 ± 0.98	1.59 ± 0.22	0.82 ± 0.29	0.60 ± 0.07	0.23 ± 0.03	70.86 ± 2.85	36.51 ± 1.29	34.34 ± 1.74	1.06 ± 0.04
Y1	10 mg kg ⁻¹ BW	5.20 ± 1.18	1.76 ± 0.27	1.04 ± 0.37	0.61 ± 0.07	0.29 ± 0.04	70.43 ± 1.40	35.60 ± 1.14	34.83 ± 0.39	1.02 ± 0.03
Y2	50 mg kg ⁻¹ BW	6.61 ± 0.73**	1.91 ± 0.30	0.59 ± 0.13	0.60 ± 0.07	0.43 ± 0.09**	1.57 ± 1.62	36.54 ± 0.98	35.03 ± 1.38	1.04 ± 0.05
Y3	200 mg kg ⁻¹ BW	6.44 ± 0.36**	1.69 ± 0.36	0.63 ± 0.13	0.58 ± 0.08	0.36 ± 0.05**	69.86 ± 2.79	35.99 ± 1.27	33.87 ± 1.75	1.06 ± 0.04
Adult										
A0	0 mg kg ⁻¹ BW	5.73 ± 1.57	1.65 ± 0.35	0.84 ± 0.30	0.62 ± 0.10	0.26 ± 0.06	70.43 ± 2.70	35.66 ± 1.35	34.77 ± 1.71	1.03 ± 0.04
A1	10 mg kg ⁻¹ BW	5.13 ± 1.09	1.72 ± 0.25	0.72 ± 0.20	0.67 ± 0.06	0.27 ± 0.06	70.71 ± 3.64	35.34 ± 1.67	35.37 ± 2.23	1.00 ± 0.04
A2	50 mg kg ⁻¹ BW	4.88 ± 0.88	1.83 ± 0.37	0.52 ± 0.11	0.64 ± 0.07	0.29 ± 0.05	72.17 ± 2.23	35.67 ± 1.03	36.50 ± 2.35	0.98 ± 0.08
A3	200 mg kg ⁻¹ BW	5.06 ± 0.36	1.61 ± 0.28	0.82 ± 0.37	0.59 ± 0.07	0.24 ± 0.05	68.86 ± 2.54	34.54 ± 1.58	34.31 ± 1.60	1.01 ± 0.06
Group	Exposure dose	ALT [U L ⁻¹]	AST [U L ⁻¹]	ALT/AST	TBIL [μmol L ⁻¹]	LDH [U L ⁻¹]	HBDH [U L ⁻¹]	CK [U L ⁻¹]	BUN [mmol L ⁻¹]	Crea [μmol L ⁻¹]
Youth										
Y0	0 mg kg ⁻¹ BW	47.57 ± 4.83	209.14 ± 31.91	0.23 ± 0.04	1.27 ± 0.21	1852.86 ± 467.30	890.43 ± 344.28	2792.00 ± 294.97	6.93 ± 1.08	52.57 ± 5.32
Y1	10 mg kg ⁻¹ BW	44.43 ± 7.68	179.71 ± 36.59	0.25 ± 0.06	1.23 ± 0.19	1731.29 ± 306.55	770.71 ± 206.29	2083.29 ± 622.24	7.13 ± 1.26	52.29 ± 3.73
Y2	50 mg kg ⁻¹ BW	54.43 ± 7.09	152.14 ± 28.20**	0.37 ± 0.07**	1.47 ± 0.18	1313.86 ± 346.95	510.86 ± 168.34**	2154.43 ± 914.55	6.49 ± 1.10	52.86 ± 3.07
Y3	200 mg kg ⁻¹ BW	48.86 ± 6.39	157.57 ± 31.83**	0.32 ± 0.06*	2.11 ± 0.30**	1499.43 ± 383.68	617.28 ± 222.54*	1658.00 ± 685.07*	6.44 ± 1.11	49.71 ± 2.75
Adult										
A0	0 mg kg ⁻¹ BW	52.43 ± 6.16	170.43 ± 38.31	0.32 ± 0.07	1.81 ± 0.13	1548.86 ± 393.39	692.86 ± 328.89	2045.86 ± 520.32	5.60 ± 0.91	53.43 ± 3.10
A1	10 mg kg ⁻¹ BW	47.43 ± 5.65	178.57 ± 54.36	0.28 ± 0.05	2.09 ± 0.41	1753.71 ± 545.80	835.71 ± 439.23	2176.86 ± 777.33	6.43 ± 0.94	53.00 ± 8.74
A2	50 mg kg ⁻¹ BW	46.00 ± 5.66	167.83 ± 31.24	0.29 ± 0.08	1.90 ± 0.29	1560.33 ± 336.45	690.83 ± 232.51	1789.17 ± 459.89	8.42 ± 1.96**	54.33 ± 5.96
A3	200 mg kg ⁻¹ BW	51.57 ± 9.05	177.00 ± 19.21	0.29 ± 0.03	1.37 ± 0.50*	1647.29 ± 44.32	709.29 ± 27.40	2041.86 ± 337.52	7.26 ± 0.61*	50.29 ± 4.57

Significant difference from group Y0 (**p* < 0.05, ***p* < 0.01); significant difference from group A0 (**p* < 0.05, ***p* < 0.01).

(BUN) indicated slight injury in the liver and kidneys of adult rats treated at high doses (50 and 200 mg kg⁻¹). However, young rats were more sensitive to high-dose exposure (50 and 200 mg kg⁻¹) of TiO₂ NPs, which indicate that TiO₂ NPs can cause greater health hazard to young rats exposed to high doses. Some scientists further studied the toxicity and bio-distribution of TiO₂ NPs in long-term and low-dose exposure to evaluate the toxicity of TiO₂ NPs. Fang *et al.* [50] examined the long-term (1, 3, and 4 months) subchronic toxicity and bio-distribution of TiO₂ NPs with various sizes (25 and 80 nm). They reported that both sizes of TiO₂ NPs were mainly accumulated in the spleen and liver, and 80 nm TiO₂ NPs were also found in the lungs. It is difficult to clear TiO₂ NPs from the body, and many TiO₂ NPs were observed in the spleen and liver even after 4 months. No subchronic toxicity was observed, while varying degrees of lesions appeared in the spleen, liver, and lung. Furthermore, they also studied the long term effects of exposure routes on bio-distribution and toxicity [51]. They revealed that the bio-distribution of TiO₂ NPs depended on the exposure route, time, and size.

In brief, TiO₂ NPs have a relatively low toxicity, but exposure to high doses can cause damage to the cells and tissues. TiO₂ NPs enter the body, accumulate in various organs, and show a very slow metabolism rate. High-dose and long-time exposure of TiO₂ NPs would affect the function of major organs such as the liver and kidney. The safe dosage of TiO₂ NPs in commercial products should be noted, and it may be necessary to pay attention to the age of the user as TiO₂ NPs show more damage in youth.

Zinc oxide nanoparticles

ZnO NPs have been widely applied because of their unique physicochemical properties [52–54]. They are traditionally used in sunscreens owing to their ability to filter UV rays strongly [55]. In addition, they are an attractive candidate for sensors because of their excellent electrochemical activity [56,57]. Moreover, zinc is an important essential trace element in human beings. Therefore, ZnO NPs are widely used as food additives and nutritional supplements [56,57]. Hence, it is necessary to study the related bio-toxicity of ZnO NPs.

In vitro studies

The results of the present study suggested that ZnO NPs had higher toxicity compared with other MONPs. According to the results of cell counting kit-8 assay performed by Wang *et al.* [31,58], after exposure of GES-1 (human gastric epithelial) cells to 25 mg L⁻¹ ZnO NPs for 24 h, the rate of cell death was as high as 80%. However, cell viability was

above 80% after exposure to 200 mg L⁻¹ TiO₂ NPs. Other reports demonstrated that ZnO NPs were toxic to a number of types of cells, such as *Tetrahymena thermophila* [59], osteoblastic MC3T3-E1 cells [60], and A549 (human lung cancer) cell line [61]. Chen *et al.* [62] investigated the cellular response induced by ZnO NPs in human umbilical vein endothelial cells (HUVECs). They found that 240 μmol L⁻¹ ZnO NPs induced relatively higher levels of ROS in HUVECs compared with CeO₂ NPs treated at the same dosage after 8 h of incubation. Quantitative analysis showed that the ROS level of ZnO NPs-treated group increased significantly at doses higher than 120 μmol L⁻¹ (Fig. 2). ZnO NPs can induce loss of cell viability, increase in ROS, DNA damage, and apoptosis [63]. The physical properties (size and shape) of ZnO NPs would have an impact on their toxicity. It has been observed that ZnO NPs (approximately 100 nm) had higher bio-toxicity than bulk ZnO (approximately 5 μm) [64]. Rod shaped ZnO NPs induced greater toxicity than spherical ZnO NPs. Different sizes and shapes would affect the interaction between ZnO NPs and cells exhibiting the size- and shape-dependent toxicities of ZnO NPs. In addition, the release rates of Zn²⁺ ions are different for different ZnO NPs [65].

In vivo studies

Since ZnO NPs are often used in cosmetics, its toxicity on the human skin is worthy of attention. The potential toxicity of ZnO NPs present in sunscreens is due to their small size as well as their ability to escape immunologic defense mechanisms, form complexes with proteins, and induce ROS formation [66]. Toxicity of ZnO NPs can occur at two different levels: first, at the skin barrier constituted by cells; second, after reaching the tissues from systemic circulation. The ability of ZnO NPs to penetrate the skin barrier was studied by many scientists. Cross *et al.* [67] reported the dermal absorption of ZnO NPs. When Franz-type diffusion cells were exposed to a sunscreen formulation containing ZnO NPs for 24 h, no ZnO NPs penetration was observed. Moreover, electron microscopy results indicated that no NPs were detected in the lower stratum corneum or viable epidermis. Filipe *et al.* [68] studied the penetration of ZnO NPs into normal and psoriatic human skin *in vivo*. They revealed that when the human skin was exposed to three marketed sunscreens containing ZnO NPs for 2 h, these NPs were only detectable in the stratum corneum. There were no ZnO NPs in the deeper skin layers, even after 48 h exposure to the sunscreens, under occlusion. To date, there is no evidence that ZnO NPs can penetrate the skin barrier to enter the cell or deeper tissues. However, some

Figure 2 ROS levels in HUVECs after exposure to NPs. (a–l) Fluorescence microscope images of intracellular ROS induced by NPs. HUVECs were treated with ZnO NPs/CeO₂ NPs (240 μmol L⁻¹) for 8 h; then the endoplasmatic reticulum (ER) and ROS were stained. (m) Image from ZnO NPs-treatment group shows the segmentation process of high-content analysis (HCA) method. (n) Quantitative analyses of ROS levels by HCA after HUVECs were treated with NPs for 8 h. Data is expressed as mean ± SD, (# $p < 0.01$ compared with that in blank, $n = 6$). Bars: 10 μm). The white arrows show bright and aggregated ER in ZnO NPs-treated cells. Reprinted with permission from Ref. [62], Copyright 2014, American Chemical Society.

researchers reported the phototoxicity of bulk and ZnO NPs in *Caenorhabditis elegans* nematode [66]. Phototoxicity is an irritation reaction to sunlight caused by chemical substances in the skin. All the results of previous studies showed that the phototoxicity of ZnO NPs was significantly enhanced under natural sunlight, and they were more likely to induce phototoxicity than bulk ZnO particles. Jang *et al.* [69] observed the phototoxicity of ZnO NPs at the tested concentrations with the 3T3 (mouse fibroblast cell) neutral red uptake test. The mechanism of phototoxicity involves the absorption of photons with energy similar to the band

gap energy by the ZnO NPs as well as the generation of hole/electron pairs and consequently ROS, which can cause damage to the cells and organs [54].

ZnO NPs are also widely applied in food additives. They have been used as a dietary supplement in humans and animals because zinc can stimulate the immune system and exert anti-inflammatory effects [70,71]. Therefore, oral toxicity has attracted much attention recently. Sharma *et al.* [72] reported that significant accumulation of NPs in the liver following sub-acute oral exposure of ZnO NPs (300 mg kg⁻¹) for 14 consecutive days leads to cellular injury.

These results were supported by the findings of Ko *et al.* [73]. They reported sub-acute oral dose toxicity of 100 nm ZnO NPs administered to rats by gavage at 0, 500, 1,000, and 2,000 mg kg⁻¹ day⁻¹ for 14 days. Their results showed significant changes in clinical signs, body weight, hematology, histopathology, and serum biochemistry at doses higher than 500 mg kg⁻¹ day⁻¹.

In summary, ZnO NPs cannot penetrate the skin barrier easily and enter the organisms; however, their phototoxicity has been confirmed. They can enter the organism by direct oral exposure leading to tissue injury.

Iron oxide nanoparticles

Owing to excellent biocompatibility, IONPs have been frequently used in biomedical fields [74–76]. The term IONPs include both superparamagnetic iron oxide nanoparticles (SPION) and magnetic IONPs, among which hematite (α -Fe₂O₃), maghemite (γ -Fe₂O₃), and magnetite (Fe₃O₄) are the most common. Maghemite (γ -Fe₂O₃) and magnetite (Fe₃O₄) are by far the most commonly employed magnetic nanoparticles for biomedical applications. IONPs are well developed and designed to be used in biosensors, magnetic resonance imaging (MRI), labeling and sorting of cells, tissue-specific release of therapeutic agents, and separation of biochemical products [77,78]. Exploring the toxicology of IONPs is the foundation for their safe and wide application.

In vitro studies

IONPs possess great biocompatibility and are similar to endogenous iron. Hence, they were considered non-toxic in the beginning. However, with the development of synthesis technology, various nanostructures of IONPs were synthesized and widely applied. The toxicity of IONPs is determined by different factors such as shapes, sizes,

coating layers, and functional groups. Many studies have already shown that IONPs induce cytotoxicity. Cai *et al.* [79] reported that polyethylenimine (PEI)-coated IONPs were more toxic than polyethylene glycol (PEG)-coated IONPs owing to the strong electrostatic interaction between the negatively charged cell surface and positively charged IONPs, though PEI might be a disturbing factor in this case. Berry *et al.* [80] observed that uncoated/dextran-coated Fe₃O₄ NPs induced vacuole formation and disrupted the clearance function of the skeleton of dermal fibroblasts, and they were able to cause varying degrees of cell death. Similarly, Stroh *et al.* [81] confirmed that a huge amount of citrate-coated γ -Fe₂O₃ NPs in cells resulted in a significant increase of protein oxidation and ROS level. The toxicities of IONPs with different surface coatings *in vitro* are shown in Table 2. The results indicated that the toxicity was also size-, shape-, dose-, and time-dependent [82–89]. Many studies presently performed on toxicity evaluation are far away from reaching a conclusion and providing guidance for the safe application of IONPs. Therefore, we should consider a more comprehensive cytotoxicity evaluation for the synthesis and utilization of these NPs.

In vivo studies

Many reports indicate that IONPs can easily accumulate in the tissues by various exposure routes. IONPs administered via intravenous route were found to accumulate in the liver, spleen, testis, lung, and brain [90]. Gu *et al.* [91] found that excess iron accumulated in the indicated organs 24 h after intravenous injection (5 mg Fe kg⁻¹) of PEG-phospholipid-coated IO nanocrystals. And a large quantity of iron-containing degradation products from the IONPs was stored in the spleen after intravenous injection (5 mg Fe kg⁻¹) (Fig. 3). Zhu *et al.* [92] intratracheally (i.t.)

Table 2 Toxicities of IONPs with different surface coatings *in vitro*

Coating material	Cell types	Size (nm)	Concentration	Incubation time	Result
Dextran	Macrophages (human)	100–150	0.1 mg mL ⁻¹	7 days	20% cell viability after 7 days [82]
	Primary peritoneal macrophages (rats and mice)	20, 60	0.2–20 μ mol L ⁻¹	15 min–2 days	Increased anti-inflammatory cytokines, reduced pro-inflammatory cytokines [83]
Poly (vinyl alcohol)	L929 (mouse fibroblasts)	82	0.2–20 mmol L ⁻¹	2 days	Toxicity depends on nanoparticles shape and size [84]
Amine-surface	HepG2 (human liver cancer cell)	61–127	0.03–3000 μ g mL ⁻¹	5 days	High positive charge causes severe cytotoxicity [85]
Tween	macrophages J774 (mouse)	30	25–500 μ g mL ⁻¹	1–6 h	Dose- and time-dependent damage [86]
Silica	A549 (human lung cancer cell)	30–120	10 μ g mL ⁻¹	2 days	Dose- and size-dependent damage [87]
Uncoated	A549 (human lung cancer cell)	20–30	Up to 80 μ g mL ⁻¹	18 h	No or low toxicity [88]
Uncoated	BRL 3A (rat liver derived cell)	30, 47	Up to 250 μ g mL ⁻¹	1 days	No toxicity up to 100 μ g mL ⁻¹ , significant toxic effects at 250 μ g mL ⁻¹ [89]

Figure 3 *In vivo* accumulation, degradation, and clearance of IONPs in mice. (a) Iron distributed in the liver, spleen, lung, kidney and brain after intravenous injection (5 mg Fe kg^{-1}) of PEG-phospholipid-coated IO nanocrystals for 24 h, prepared via the organometallic route (sizes of ~ 5 , ~ 15 , and $\sim 30 \text{ nm}$), and Feridex (is a dextran-coated cluster of IONPs approved as a contrast agent for hepatic imaging). (b, c) Percent of IONPs (percent superparamagnetic/ferrimagnetic content) remaining in liver (b) and spleen (c). Reprinted with permission from Ref. [91], Copyright 2012, American Chemical Society.

instilled $22 \text{ nm } ^{59}\text{Fe}_2\text{O}_3$ NPs (4 mg/rat) into rats. They found that $^{59}\text{Fe}_2\text{O}_3$ NPs can pass through the alveolar-capillary barrier and enter into the systemic circulation in 10 min. $^{59}\text{Fe}_2\text{O}_3$ NPs were taken up by the lung tissues and further distributed to the liver, spleen, and kidneys. Bellusci *et al.* [93] also found presence of iron in the liver, spleen, lung, and brain after inhalation of IONPs. The highest iron concentrations were observed in the liver and spleen. Small IONPs ($<10 \text{ nm}$) can be rapidly removed through extravasation and renal clearance, while large IONPs ($>200 \text{ nm}$) were sequestered by the spleen via mechanical filtration [94].

Various physicochemical factors of IONPs, such as surface chemistry, size, shape, and charge, also play a very crucial role in the toxicity of IONPs in animal studies [95,96]. Zhu *et al.* [97] confirmed that Fe_2O_3 NP exposure can induce increased ROS level in the lungs after i.t. instillation of two sizes of Fe_2O_3 particles (22 and 280 nm). *In*

vivo studies have shown improved penetration of positively charged IONPs through the placenta compared with negatively charged IONPs in CD-1 mice [98]. Additionally, the tissue or cell type is another important factor that influences the toxicity response of IONPs. Hanini *et al.* [99] showed that IONPs can induce toxicity in the liver, kidney, and lung *in vivo*, while the brain and heart remained unaffected. In conclusion, the toxicity of IONPs is related to their physicochemical properties, such as surface chemistry, size, and shape. Further study needs to be performed on their biological toxicity.

Other MONPs

Some studies focused on other MONPs, such as CuO , Al_2O_3 , CoO , and NiO NPs [100–103]. Sun *et al.* [100] reported that CuO NPs cause significant apoptosis of A549, H1650, and CNE-2Z cell lines. Furthermore, they pointed out that the cytotoxicity of CuO NPs may involve the autophagic pathway. Dong *et al.* [101] studied the toxicity of Al_2O_3 NPs. Their results showed that the toxicity of Al_2O_3 NPs was considerably low, although these particles are easily internalized into the cells. However, CoO and NiO NPs induce significant cytotoxicity [102].

MECHANISM STUDY

From the above, we can see that different MONPs have different toxicities. The mechanism underlying of the toxicity is still controversial. However, scientists have summarized some general principles for the toxicity of NPs based on results of all researches performed as follows: (i) toxicity of larger NPs is less than the smaller ones; (ii) in eukaryotes, NPs can cross and damage the biomembranes; (iii) oxidative stress is often caused by NPs; (iv) chemical compositions of NPs are closely connected to their toxicity; and (v) in prokaryotes, NPs often remain outside the cells, while in eukaryotes, they can enter into the cells or even the organisms [104,105]. At present, the toxicity mechanism is mainly divided into ROS-mediated apoptosis and non-ROS-related toxicity.

ROS-mediated toxicity

Cellular mechanisms

As is already known, increased levels of ROS, including free radicals such as the superoxide anion, hydroxyl radicals, and non-radical hydrogen peroxide, activate oxidative stress, which results in lipid peroxidation and cell membrane damage. Subsequently, the normal cell functions are lost leading to cell death or apoptosis [102,106]. ROS-

mediated cytotoxicity is one of the most recognized toxicity mechanisms of MONPs [13,107,108]. There are several factors that induce the production of ROS by MONPs: (i) prooxidant functional groups on the reactive surface of NPs; (ii) active redox cycling on the surface of NPs; and (iii) NPs-cell interactions [13,109].

Many studies have confirmed that ROS is generated on exposure to MONPs, including ZnO, TiO₂, Fe₃O₄, and Fe₂O₃ NPs [110–113]. Xiong *et al.* [110] detected that TiO₂ and ZnO NP suspensions were able to generate ·OH. Keratinocyte HaCaT cells exposed to 30 mg mL⁻¹ TiO₂ NPs for 24 h, showed 150%–200% increase in intracellular ROS compared with the untreated control [112]. The treatment of HepG2 (human hepatocarcinoma) cells with 20 mg mL⁻¹ ZnO NPs for 6 h induced a 200% increase in ROS levels [113]. High ROS levels can damage the cells by peroxidizing lipids, resulting in decline of physiological function and cell apoptosis or death. The cell membrane includes a lipid bilayer, and lipids are the primary target of ROS attack [88,114]. The deterioration of cell membrane causes extensive damage, which ultimately leads to cell death. Karlsson *et al.* [88] revealed that extensive lipid peroxidation was detected when A549 cells were exposed to TiO₂, ZnO, Fe₃O₄, and Fe₂O₃ NPs. The cellular amount of malondialdehyde (MDA) and release of LDH from the cells reflected lipid peroxidation and membrane damage increased. As iron (Fe) and copper (Cu) are transition metals, IONPs and CuO NPs can generate oxidative stress via Fenton-type reactions [111]. Therefore, the release of Cu- and Fe-ion from the surface by enzymatic degradation is another reason for ROS generation.

Molecular mechanisms

Many studies have demonstrated that ROS can cause DNA damage. Damaged DNA elicits the activation of an important transcription factor, p53 [115]. When activated, p53 would upregulate the expression of Bax. In addition, p53 downregulates the expression of Bcl-2, an anti-apoptotic protein, which competes with Bax protein, leading to a decrease in the amount of heterodimer Bcl-2 to inhibit Bax function [116–118]. Bax, in turn forms a homodimer complex and induces pore formation in the lipid bilayer of mitochondrial membrane [119], and subsequently the apoptotic pathway is triggered. Song *et al.* [120] studied the oxidative DNA damage induced by MONPs in mice. Their results showed that DNA damage in the liver is dramatically enhanced. Li *et al.* [114] observed the suppression of Bcl-2 protein and genes followed by cytochrome c release, increasing caspase-3 and -9 in the spleen of TiO₂ NPs-treated

mouse.

In addition, high ROS levels would alter the permeabilization of mitochondrial membrane. Consequently, cytochrome c, a pro-apoptotic protein is released, and it then binds to procaspase-9 to activate caspase-9. The activation of caspase-9 in turn stimulates the release of caspase-3, which mediates the cell death process [121,122]. Manke *et al.* [123] reported cell apoptosis due to cerium oxide (CeO₂) NP exposure, and they observed a distinct increase in ROS levels followed by decrease in mitochondrial membrane potential and release of caspase-9 and -3.

Non-ROS-mediated toxicity

Besides the mechanism of ROS-induced cytotoxicity, some researchers found that the excessive accumulation of low-toxicity materials such as TiO₂ NPs on the cell membrane is another important reason for cytotoxicity. [31,124–126]. Recently, Wang *et al.* [31] reported that excess TiO₂ NPs on the cell surface is the major trigger for cytotoxicity. They demonstrated that the excess NPs attached on the cell membrane block the ion pathway, influence ion exchange, disrupt the exocytosis process, and finally lead to cell death. IONPs are magnetically targeted to a tissue/organ, and the high concentration of IONPs on the surface of the tissue/organ could induce toxicity [126].

In addition, the ions released from MONPs are related to cytotoxicity [126,127]. Many studies have confirmed that dissolved zinc ions of ZnO NPs significantly increased bio-toxicity. Excess Zn²⁺ can lead to an imbalance in homeostasis causing damage to the lysosomes and mitochondria, which in turn leads to cell death [59,128,129]. Some nanomaterials are intended for therapeutic purpose such as drug delivery. These nanomaterials are always designed to bind to specific receptors on the cell membrane. Binding of these nanomaterials to death receptors might lead to cell death by inducing a signal complex, which cleaves caspase-3 and activates caspase-8. Subsequently, cellular content degradation is initiated [130]. Zhao *et al.* [131] reported that TiO₂ NPs can activate caspase-8 in JB6 mouse epidermal cells. Cui *et al.* [132] observed an increase of Toll-like receptors (TLR2 and TLR4) in mouse after TiO₂ NP exposure. The activation and increase of these receptors can induce inflammatory response and cell apoptosis. We summarize the bio-toxicity of MONPs *in vitro* and *in vivo* and their toxicity mechanism in Fig. 4.

COMBINED TOXICITY EVALUATION OF MONPs

Owing to the extensive use of MONPs in industrial and

Figure 4. Schematic diagram of MONP toxicity and mechanism. *In vitro* toxicity of MONPs is mainly caused by the damage of mitochondrial/DNA/protein and phospholipid bilayer, leading to cell toxicity. *In vivo* toxicity is caused by penetration of MONPs into the blood circulation through inhalation, oral, and dermal routes, and these MONPs finally reach the main organs of the body causing organ damage. Some nanomaterials also cause phototoxicity on the skin. MONP toxicity is induced mainly by four ways: the generation of ROS, effect of released ions, excessive accumulation of NPs on the cell surface, and combination of NPs with specific death receptors.

consumer products, a variety of NPs are released into the environment. They are always in the form of a mixture. Previous studies performed to understand the behavior and risks of NPs are mostly limited to single NPs. However, these NPs may undergo complex physical and chemical transformations, like dissolution, complexation, adsorption, dispersion, and aggregation, influencing their respective fate and toxicity potential when used in industrial and consumer products. Therefore, studies on the fate and toxicology change of NPs in combined systems are attracting increasing attention of scientists worldwide.

Combined toxicity between TiO₂ and ZnO NPs

TiO₂ and ZnO NPs, two semiconductor MONPs, are among the most extensively used MONPs in industry.

The annual production volume and the predicted environmental concentrations of TiO₂ and ZnO NPs are significantly higher than those of other frequently studied MONPs. Coupled with their wide and similar applications in personal-care products and industry, the interactions between these two NPs are worth investigating. Tong *et al.* [133] studied the chemical interactions between TiO₂ and ZnO NPs in water matrix. Their results demonstrated that the presence of TiO₂ NPs influenced the dissolved zinc released from ZnO NPs in the solution. In the presence of TiO₂ NPs, Zn (II)-TiO₂ surface complexes are formed, which decrease the level of the free Zn ions in the solution, thereby reducing the toxicity of ZnO NPs. The toxicity of soluble ZnO NPs and chemically stable TiO₂ NPs in combination was analyzed by monitoring the bacterial cell

Figure 5 Cytotoxicity evaluation of ZnO NPs (15 mg L⁻¹), Vc (300 mg L⁻¹), and ZnO NPs plus Vc treatment for 24 h (a, b). Cell viability of gastric epithelial cell line (GES-1) (a), and neural stem cell line (NSCs) (b) after 24 h co-incubation with ZnO NPs, Vc, and ZnO NPs plus Vc treatment. * $p < 0.05$ compared with cells exposed to ZnO NPs. Cell viability after treatment of various concentrations of ZnO NPs (c), various concentrations of CPP (d); (e) the effect of CPP (500 mg L⁻¹) at various concentrations of ZnO NPs; (f) cell counts after treatment with 20 mg L⁻¹ ZnO NPs, 500 mg L⁻¹ CPP, 20 mg L⁻¹ ZnO NPs & 500 mg L⁻¹ CPP, respectively; (g) the effects of various concentrations of CPP and ZnO NPs (20 mg L⁻¹); (h) the effects on LDH release at various concentrations of CPP with ZnO NPs (20 mg L⁻¹). # $p < 0.05$ compared with control group; * $p < 0.05$ compared with cells exposed to ZnO NPs. Reprinted with permission from: (a, b) Ref. [58], Copyright 2014, Royal Society of Chemistry; (c–h) Ref. [135], Copyright 2014, Royal Society of Chemistry.

membrane integrity and adenosine triphosphate (ATP) levels. Results show that there is reduced contact between TiO₂ NPs and bacteria in the presence of both ZnO NPs and dissolved zinc. However, this inhibitory effect of ZnO NPs on the adsorption of Zn²⁺ is reduced by TiO₂ NPs [134]; these provide the first evidence that interactions between multiple MONPs alter the toxicity of the individual NPs in unexpected ways. Therefore, we should pay particular attention to the combined toxicity of MONPs.

Combined toxicity of MONPs in food additives

Currently, the safety evaluation standards for MONPs as food additives are only based on the toxic effects of a single additive. However, when MONPs are used in a complex system with other food additives, toxicity may be dramatically influenced owing to various combined effects. However, only a few reports focus on the combined toxicity. Wang *et al.* [58] reported a combined toxicity study of ZnO NPs and vitamin C (Vc) in food additives. The results showed that Vc increased cytotoxicity significantly compared with single ZnO NPs (Fig. 5a, b). Moreover, a significant increase in toxicity was also observed in *in vivo* experiments. Injury to the liver and kidney was detected after repeated oral exposure to ZnO NPs plus Vc in mice. However, another type of food additive, casein phosphopeptides (CPP), showed significant cytoprotective effects against cytotoxicity induced by single ZnO NPs (Fig. 5c–h) [135]. The cytotoxicity of TiO₂ NPs seems far less affected in a complex system containing Vc or CPP. Based on these results, we can suggest that different MONPs show different toxicity change trends in different complex systems. The nanotoxicology of the complex system requires more attention to fill the gap of nanosafety study.

CONCLUSIONS AND PERSPECTIVE

In this review, we systematically summarized the toxicity effects of the most widely used MONPs both *in vitro* and *in vivo*. Many factors such as the size, shape, and surface chemical property have an influence on the toxicity of MONPs. Meanwhile, various exposure routes affect toxicity and bio-distribution *in vivo*. However, to date, determining the characteristics that are responsible for the hazardous nature of some NPs remains a huge challenge, and it is critical in determining the practical application of MONPs. The toxicity of MONPs remains debatable. The assays currently used for toxicity evaluation of IONPs are still not well adapted for these measurements, and many results are even published based on unreliable methods. Therefore, a unified methodology for toxicity evaluation of

MONPs needs to be developed further. Moreover, there are only very few reports on the combined effects of MONPs so far. The safety evaluation standards for MONPs used in commercial products are always set up based on the toxic effects of single MONPs alone. However, since size, chemical nature, and surface properties have a dramatic influence on the toxicity of nanomaterials, toxicity effect may change when MONPs are used in consumer products such as cosmetics, food, and environment. The results of combined toxicity in food show that the toxicity of ZnO NPs dramatically changed both *in vitro* and *in vivo* in different complex systems. However, TiO₂ NPs, which are chemically inert, seems far less toxic, even in a complex system. Therefore, various MONPs show different toxicity change trends in different complex systems. For the safety assessment of MONPs used in commercial products, nanotoxicological study of the composite systems requires more efforts in the future.

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Conflict of interest The authors declare that they have no conflict of interest.

Yanli Wang is now working at the Institute of Nanochemistry and Nanobiology of Shanghai University as an associate professor since 2012. She obtained her PhD degree in environmental engineering from Shanghai University in 2010. Her research interests include bio-effects and safety evaluation of nanomaterials and their application in bio-imaging and cancer therapy.

Minghong Wu obtained her PhD degree from Shanghai Institute of Applied Physics of Chinese Academy of Sciences in 1999. She is the National outstanding youth and Yangtze River scholar of China. Based on her scientific contribution, she was selected as the Russian Academy of foreign academicians of Russian Academy of Engineering in 2008 and Russian Academy of Science in 2015. Her research interests mainly focus on bio-effects and safety evaluation of nanomaterials and environmental pollution analysis and control.

金属氧化物纳米颗粒生物毒性效应及毒性机理研究进展

王艳丽^{1,2}, 丁琳¹, 姚晨婕¹, 李晨晨¹, 邢晓军¹, 黄雅男¹, 顾天骄¹, 吴明红^{1*}

摘要 纳米材料由于其独特的性质已经被广泛应用于很多领域,但随着纳米材料的大规模制备和广泛应用,它对环境以及人类的潜在危害越来越引起人们的重视.金属氧化物纳米颗粒(MONPs)作为一类纳米材料大量地用于食品、医药、化妆品、传感器等领域.因此,MONPs的生物毒性研究至关重要.本文主要对目前应用最为广泛的几种MONPs(纳米二氧化钛、氧化锌、氧化铁等)生物毒性的研究及其毒性机理做了总结. MONPs导致毒性的机制有两个方面: ROS介导的毒性和非ROS介导的毒性. ROS激活氧化应激,导致脂质过氧化,引起细胞膜损伤,此外, ROS可以激活caspase-9和caspase-3,触发凋亡通路. 非ROS介导的毒性机制,包括MONPs释放的离子引起的毒性,纳米粒子在细胞表面的粘附以及与特定的死亡受体的相互作用. 此外,由于当纳米材料处于一个复杂的体系中时,它自身的性质,包括尺寸、粒径、表面化学性质等都会发生变化,我们对一些MONPs的复合毒性也做了讨论.