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REVIEW

Toxic effects of the interaction of titanium dioxide nanoparticles with chemicals or physical factors

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Abstract: Due to their chemical stability and nonallergic, nonirritant, and ultraviolet protective properties, titanium dioxide (TiO_2) nanoparticles (NPs) have been widely used in industries such as electronics, optics, and material sciences, as well as architecture, medicine, and pharmacology. However, increasing concerns have been raised in regards to its ecotoxicity and toxicity on the aquatic environment as well as to humans. Although insights have been gained into the effects of TiO_2 NPs on susceptible biological systems, there is still much ground to be covered, particularly in respect of our knowledge of the effects of the interaction of TiO_2 NPs with other chemicals or physical factors. Studies suggest that interactions of TiO_2 NPs with other chemicals or physical factors may result in an increase in toxicity or adverse effects. This review highlights recent progress in the study of the interactive effects of TiO_2 NPs with other chemicals or physical factors.

Keywords: titanium dioxide, TiO_2, nanoparticles, interaction, chemicals, physical factors

Introduction

Nanoparticles (NPs) are raw materials used in nanotechnology, with a size range of 1–100 nm in no less than one of their three dimensions.[1–3] Titanium dioxide (TiO_2) NPs consists of three polymorphs, including anatase, rutile, and brookite.[4] TiO_2 NPs have been widely used in many products, such as toothpastes, sunscreens, cosmetics, food products, pharmaceuticals, and nanomedical reagents.[5] TiO_2 particles have been considered as nontoxic mineral particles and traditionally used in the fields of cosmetics, food, and drugs. They were even used as "dust negative control" in many in vitro and in vivo toxicological investigations for many years.[3,6] However, research evidence suggests that TiO_2 NPs may possess higher toxicity potential than their bulk materials.[5,7,8] Zhao et al[8] found that TiO_2 NPs caused higher cytotoxicity than fine particles in cell culture. Due to their very small size, NPs can penetrate basic biological structures, which may, in turn, disrupt their normal function.[3,9] Recent research evidence shows that TiO_2 NPs may induce cellular toxicity effects in cardiac tissue.[10] The toxicity effects of TiO_2 particles were also observed in cells of the circulatory system. Li et al[6] found that the erythrocytes treated with TiO_2 NPs underwent abnormal sedimentation, hemagglutination, and hemolysis, which were totally different from those treated with TiO_2 fine particles. Lung tumors were also found in rats after lifetime exposure to high concentrations of TiO_2 particles.[11] Moreover, a recent study showed oxidative stress in mice brain as well as overproliferation of all glial cells.[12] These occurred in mice that were exposed to 2.5 mg/kg, 5 mg/kg, and 10 mg/kg body weight TiO_2 NPs through nasal administration for 90 days. The toxicokinetics (Figure 1) and toxic effects of

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TiO_2 NPs[13–15] alone have been well documented in many in vivo and in vitro studies, but reviews of the effects (or toxicities) of the interaction of TiO_2 NPs with other chemicals or physical factors are currently unavailable. TiO_2 NPs may coexist with other chemicals or physical factors in the surrounding environment and occupational settings. In the field of nanomedicine, TiO_2 NPs are being used as drug carriers.[3] Therefore, evaluating the interactive effects of TiO_2 NPs with other chemicals or physical factors is vital for the safe application of TiO_2 NPs. This review will mainly focus on the current knowledge concerning the effects of the interaction of TiO_2 NPs with other chemicals or physical factors and will identify areas where further improvement is needed.

Effects of TiO_2 NP interaction with metals and their compounds

With growing applications, TiO_2 NPs are rapidly entering the aquatic environment,[16] and thus the aquatic environment is expected ultimately to be a sink for the sedimentation of these NPs. Consequently, these NPs will inevitably mix and interact with other aquatic pollutants, including metals and their compounds.[17] In addition, NPs have been found to be capable of absorbing and separating metals from aqueous or organic solutions.[18,19]

TiO_2 NPs have been tested as a sorbent in the solid-phase extraction for preconcentrated lead (Pb) in river water and seawater.[20–22] Zhang et al[20] investigated the potential acute toxicity of the interaction between TiO_2 NPs (50 nm and 120 nm) and lead acetate (PbAC) in mice. Suspensions of TiO_2 NPs (5 g/kg body weight) alone, PbAC (500 mg/kg) alone, and TiO_2 NPs (5 g/kg) plus PbAC (500 mg/kg) were administered to mice via oral gavage, respectively. No synergistic acute toxicity in mice was found after treatment with the combination of TiO_2 NPs and PbAC. However, Du et al[23] found that, compared with the control (1% dimethyl sulfoxide), mixtures of TiO_2 NPs of different doses (21 nm, 80% anatase, 20% rutile) plus PbAC (1 μg/mL) induced a significant increase in reactive oxygen species (ROS) generation (at 0.001 μg/mL, 0.01 μg/mL, 0.1 μg/mL, 1 μg/mL, and 10 μg/mL of TiO_2), intracellular superoxide dismutase (SOD) activity (at 0.1 μg/mL and

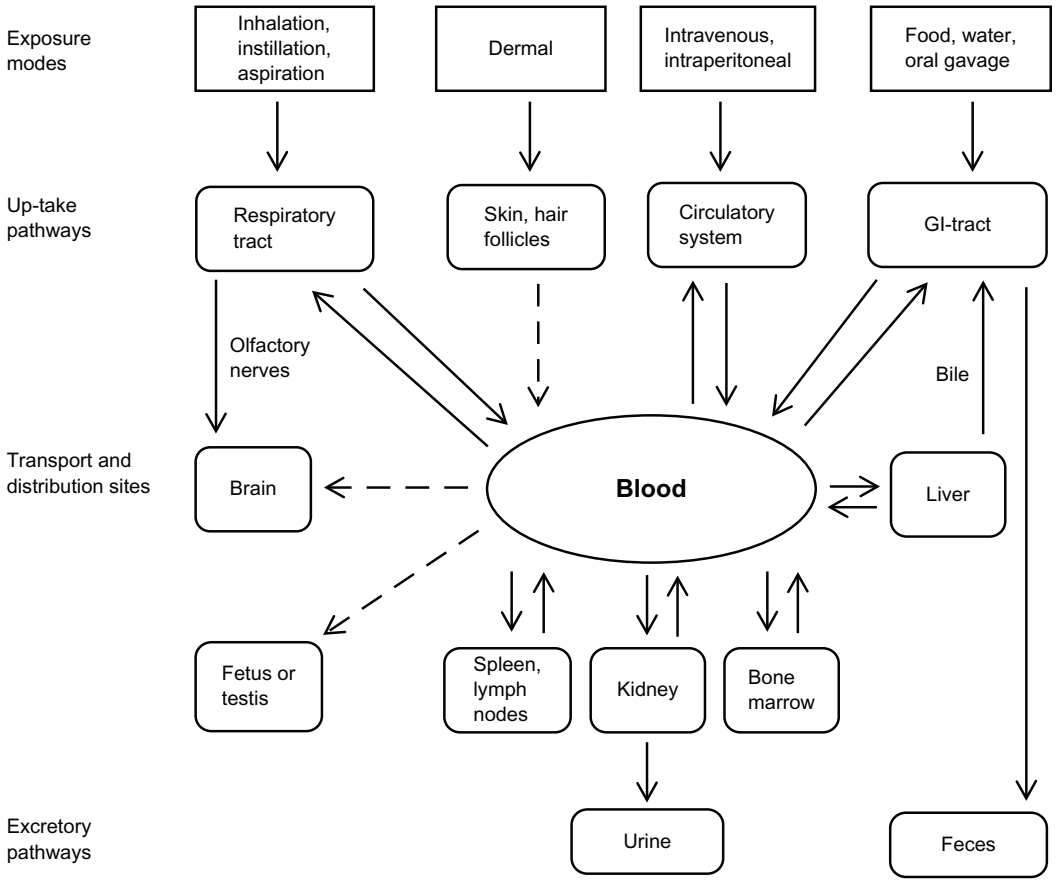

Figure 1 Toxicokinetics and accumulation sites of titanium dioxide nanoparticles.
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Abbreviation: GI, gastrointestinal.

0.01 μg/mL of TiO_2), glutathione (GSH) levels (at 0.01–1 μg/mL of TiO_2), 8-hydroxydeoxyguanosine levels (at 1 μg/mL and 10 μg/mL of TiO_2), 8-oxoguanine DNA glycosylase homologue 1 expression (at 0.001–1 μg/mL of TiO_2), and cytotoxicity (at 0.1 μg/mL, 1 μg/mL, and 10 μg/mL of TiO_2) in human embryo hepatocyte cells. These results suggest that interaction of TiO_2 NPs and PbAC may result in an increase of oxidative stress in culture cells.

Arsenic (As) is a metalloid. Chronic As exposure could cause cancer, neuropathies, and bronchopulmonary, cardiovascular, and metabolic diseases.[24] To reduce As pollution, TiO_2 NPs have been used as photocatalytic oxidants and/or absorption materials to remove As from water,[25] which implies an interaction between As and TiO_2 NPs. Due to their small diameter, large surface area, and the ability to uptake –OH ions from solution, TiO_2 NPs could adsorb metal ions through electrostatic interaction.[26,27] Evidence shows that variables such as pH and temperature may affect the absorption and/or desorption of As (III) and As (V) by TiO_2 NPs in the aqueous solution. Pena et al[28] found that at 21°C–25°C and pH <8, TiO_2 NPs could be used to remove As (V) from solution through adsorption, but the maximum removal for As (III) occurred at about pH 7.5. Additionally, they demonstrated that the competing anions such as silicate, carbonate, and phosphate had a low effect on the adsorption capacities of TiO_2 NPs on As (III) and As (V) in a neutral pH range, which was in agreement with the results of Bang et al.[29] Niu et al found that the adsorption of As (V) was more favored in acid solution at 25°C, whereas the uptake of As (III) was preferred in alkaline solution by TiO_2 NPs at 25°C.[30] The maximum uptake of As (V) and As (III) was 208 mg/g (pH =3.0) and 60 mg/g (pH =7.0). Their experiments also suggested that more than 80% of As (III) and 95% of As (V) adsorbed on TiO_2 NPs could be desorbed with 1.0 M sodium hydroxide solution within 1 hour, as demonstrated by desorption tests, which was confirmed by Bang et al.[29] Jegadeesan et al[31] indicated that the capacity for sorption to As by TiO_2 NP polymorphs might be affected by sorption site density, surface area (particle size), and crystalline structure. Wang et al[32] stated that As toxicity on *Ceriodaphnia dubia* might increase when TiO_2 NPs (5–10 nm) interact with As in the ecosystem. They found that TiO_2 NPs less than 400 mg/L alone were nontoxic. The 24-hour median lethal concentration (LC_{50}) of As alone on *Ceriodaphnia dubia* was 3.68±0.22 mg/L. In addition, the presence of low concentrations of 50 mg/L TiO_2 NPs increased the toxicity of As significantly, and the LC_{50} of As was also lowered to 1.43 mg/L. In summary, available studies show that pH, temperature, composite method, and crystalline structure may all be important for the adsorption of As (III) and As (V) by TiO_2 NPs, and an alkaline environment is suitable for the desorption of As (III) and As (V). More studies are needed to investigate the toxicity effects after combination of As with TiO_2 NPs.

Copper (Cu) is an important element in human physiological processes. Exposure to low doses of Cu[33] is harmless because Cu is an essential trace element for the human body. Adverse immunotoxicological effects on human health could be caused only by an overexposure to Cu. Overexposure, especially a sublethal dose exposure of Cu, could induce immunotoxicity in mice, including cell-cycle arrest and cell death in the spleen and thymus.[34] Fan et al[35] found that TiO_2 NPs (at a concentration generally considered to be safe in the environment) remarkably enhanced the toxicity of Cu on *Daphnia magna* by increasing the bioaccumulation of Cu. In addition, they found that the Cu was adsorbed on to the TiO_2 NPs when ingested and was accumulated in the animals, thereby causing an increase in toxic effects.

Cadmium (Cd) is one of the most toxic elements to which human beings may be exposed.[36–38] Cd compounds[39] are widely used in rechargeable nickel-Cd batteries. Cigarette smoke, polluted foods, and batteries are the major sources of Cd pollution. Xia et al[40] investigated the combined toxicity of cadmium chloride ($CdCl_2$) and TiO_2 NPs (25 nm) in human embryo kidney (HEK293T) cells. They found that cotreatment with 3.8 μm/L $CdCl_2$ and 7.5 μg/mL TiO_2 NPs exerted additive effects on the cellular oxidative damage by upregulation of heme oxygenase 1 gene expression, catalase activities, and malondialdehyde concentration. A combination of $CdCl_2$ (5.12 μm/L) and TiO_2 NPs (10.05 μg/mL) showed synergetic effects on activities of SOD and ROS concentrations. Zhang et al[41] assessed the bioaccumulation of Cd in carp in the presence of TiO_2 NPs (21 nm) and found that the presence of TiO_2 NPs and the accumulation of Cd in carp was positively correlated.

Hu et al[42] investigated the combined effects of TiO_2 NPs (21 nm) and humic acid (HA) on the bioaccumulation of Cd in zebrafish. They found that the presence of TiO_2 NPs at 5–20 mg/L in water containing HA could alter the exposure of Cd and other potential heavy metals to zebrafish. The presence of TiO_2 NPs or HA alone with Cd slightly increased the uptake rate constants of Cd in fish. TiO_2 NPs have a slightly higher uptake than HA, whereas mixtures of HA and TiO_2 NPs with Cd slightly reduced the uptake rate constants. The mechanism underlying these combined effects is unclear.

Yang et al[43] investigated Cd adsorption on polyacrylate-coated TiO_2 NPs, which could decrease the concentration of Cd ion in an aquatic environment and its effect on the bioavailability as well as toxicity of Cd to green algae *Chlamydomonas reinhardtii*. They found that Cd absorbed quickly on to TiO_2 NPs (anatase, 1–10 nm), reaching a steady state within 30 minutes. Interestingly, they found that the presence of TiO_2 NPs could alleviate the Cd toxicity to the green algae cells, which might be caused by TiO_2 NP adsorption on Cd^{2+}, resulting in a decrease of free Cd ion in the medium and, further, its bioaccumulation in the algal cells. In addition, the electrostatic and potentially steric repulsions between TiO_2 NPs and algal cells might hinder their direct contact with each other and then prevent the internalization of TiO_2 NPs into the cells.

Taken together, toxicities of TiO_2 NPs alone have been well documented.[10,44,45] However, knowledge of the combined effects of TiO_2 NPs with other chemicals is limited. The existing evidence suggests that TiO_2 NPs can absorb metal ions, including Pb, As, Cu, and Cd, in the solution. Meanwhile, interaction of TiO_2 NPs and metal compounds (see Table 1) may also result in the increased toxicity demonstrated by increased oxidative stress to cells and decreased LC_{50} to aquatic organisms.[23,40] Therefore, more ecology investigations and biology experiments of their combined toxicity should be carried out.

Effects of TiO_2 NP interaction with organic and inorganic compounds

Bisphenol A (BPA) is an endocrine disruptor that can mimic estrogen and may lead to adverse health effects.[46,47] Woodruff et al[48] analyzed data for 163 chemical analytes in 12 chemical classes in subsamples of 268 pregnant women from the National Health and Nutrition Examination Survey

Table 1 Studies in vitro on the interactive effects of TiO_2 NPs with chemicals or physical factors

Reference	Supplier	Characteristics of TiO_2NP			Dispersion method	Exposure concentration (μg/mL)
		Particle size (nm)	Crystal structure	Surface area (m^2/g)		
23	Degussa	21	80% anatase, 20% rutile	49.6	10 min ultrasonication and 30 s vortex mixing	0.001, 0.01, 0.1, 1, 10
40	Degussa	25	80% anatase, 20% rutile	50	Suspended fresh immediately before use	0, 0.25, 0.5, 0.75, 1, 1.25 TU (1TU = 10.05 μg/mL)
49	Degussa	25–50	80% anatase, 20% rutile	50	Vortexed for 2 min, ultrasonicated for 10 min	0, 1, 5, 10
55	Degussa	25	80% anatase, 20% rutile	50	NA	0, 0.01, 0.1, 1
57	Degussa	21	80% anatase, 20% rutile	NA	Ultrasonicated for 40 min	0, 10
65	Degussa	20	rutile and anatase	50	Ultrasonicated for 15 min	50
66	Wanjin Material Corp; Degussa	4, 10, 21 25, or 60	anatase, rutile; anatase/rutile (3:1)	NA	Freshly prepared and diluted	0, 10, 50, 100, 200
67	Degussa	20	70%–85% anatase and 30%–15% rutile	48.08	Sonicated for 30 min	0, 1, 5
68	Sigma Chemicals, Degussa	<25, <100; 31	anatase, rutile; 86% anatase, 14% rutile	NA	Sonicated for 30 min	50, 100
71	Degussa	21	25% rutile and 75% anatase	NA	Sonicated for 10–15 min	200
75	Sigma-Aldrich	NA	anatase and rutile	NA	Sonicated for 30 min	200
82	Degussa	NA	NA	NA	NA	61, 60

Abbreviations: ↑, combined effect showed a significant increase than TiO_2 NPs group and other factor group alone; ↓, combined effect showed a significant decrease than TiO_2 NPs group and other factor group alone; ↔, combined effect showed no significant difference than TiO_2 NPs group and other factor group alone; 8-OHdG, 8-hydroxydeoxyguanosine; GSH, glutathione; *HO-1* gene, *heme oxygenase 1* gene; MMP, mitochondrial membrane potential; NA, data not available; NPs, nanoparticles; OGG1, 8-oxoguanine DNA glycosylase homologue 1; ROS, reactive oxygen species; SOD, superoxide dismutase; TiO_2, titanium dioxide; UVA, ultraviolet A ; DNA, deoxyriboNucleic acid; MDA, malondialdehyde; CAT, catalase activities; NO, nitric oxide; PARP, poly (ADP-ribose) polymerase ; MTS, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium; NAC, N-acetyl cysteine; LDH, lactic acid dehydrogenase; mRNA, messenger ribonucleic acid; BAX, Bcl-2–associated X protein; DMEM, Dulbecco's Modified Eagle's Medium; TU, toxic unit; MEM, Minimum Essential Medium; ADP, adenosine diphosphate; min, minutes; PbAC, Plumbi Acetatis; BPA, bisphenol A; HBE, human bronchial epithelial cell; NaF, sodium fluoride; h, hours; HaCaT, a cell type belonging to an immortal human keratinocyte line; RPMI, Roswell Park Memorial Institute; BCL2, B-cell lymphoma 2 protein.

2003–04, a nationally representative sample of the US population. They found that BPA was detectable in 96% of pregnant women. Therefore, interactions between TiO_2 NPs and BPA may occur when TiO_2 NPs are used as drug carriers in the human body. Zheng et al[49] evaluated the interactive effects of TiO_2 NPs (25–50 nm) with BPA on their physiochemical properties and in vitro toxicity in human embryo hepatocytes (L-02 cells). They found that TiO_2 NPs alone (0 mg/L, 0.1 mg/L, 1 mg/L, and 10 mg/L) or BPA alone (0 μmol/L, 0.1 μmol/L, 1 μmol/L, and 10 μmol/L) did not exert significant DNA and chromosomal damage, whereas the mixture of TiO_2 NPs and BPA induced a significant increase in oxidative stress, DNA double-strand breaks, and micronuclei formation in a weak synergistic manner. An increase in intracellular levels of BPA bound by TiO_2 NPs was hypothesized to be the reason behind the synergistic toxicity. This could have been determined if the investigators in this study used varying concentrations of TiO_2 NPs in the combination.

Dichlorodiphenyltrichloroethane (p,p′-DDT) was widely used as an effective insecticide, and had been proven to have genotoxicity, developmental toxicity, and endocrine-disruptive effects in human beings and a wide range of living organisms.[50–52] Therefore, the degradation of DDT had attracted great attention.[53,54] Recently, TiO_2 NPs have been tested to degrade the p,p′-DDT, which increases the risk of exposure to mixtures of TiO_2 NPs and p,p′-DDT. Shi et al[55] examined the interactive toxicities of p,p′-DDT and TiO_2 NPs (25 nm) at low concentrations in L-02 cells. The mixtures induced higher toxicity than TiO_2 NPs or p,p′-DDT alone. Combination of traces of TiO_2 NPs (0 μg/mL, 0.01 μg/mL, 0.1 μg/mL, and 1 μg/mL) and traces of p,p′-DDT (0 μmol/L, 0.001 μmol/L, 0.01 μmol/L, and 0.1 μmol/L) synergistically enhanced genotoxicity, as demonstrated by an increase in

Exposure time	Cell line	Culture medium	Combined factors/exposure condition	Combined effects
24 h	L-02	DMEM	PbAC/1 μg/mL	Cell viability↓, ROS↑, GSH↑, SOD↓, 8-OHdG↑, OGG1 expression↑
24 h	HEK293T	DMEM	$CdCl_2$/0, 0.25, 0.5, 0.75, 1, 1.25 TU (1 TU = 5.12 μmol/L)	*H0-1* gene express↑, OGG1 expression↑, SOD↓, ROS↑, MDA↔, CAT↑
24 h	L-02	DMEM	BPA/0, 0.1, 1, 10 μmol/L	Cell viability↔, ROS↑, MDA↑, DNA double strand break↑, chromosomal damage↑
12, 24, 36 h	L-02	DMEM	p,p′-DDT/0, 0.0001, 0.01, and 0.1 μmol/L	Cell viability↔, apoptosis test↔, ROS↑, MDA↑, 8-OHdG↑; DNA strand break↑; micronucleus frequency↑
72 h	16-HBE	RPMI-1640	NaF/0, 10, 20, 30 mg/L	Cell viability↔, apoptosis test↑, SOD↓, MDA↑, NO↑
1 h	HaCaT	NA	Nitrite, UVA/nitrite: 0, 0.1, 0.5, 1, 2 mM; UVA: 365 nm, 0.6 mW/cm², 1 h	Cell viability↓, apoptosis test↑, protein tyrosine nitration↑
1 h	HaCaT	MEM	UVA/365 nm, 3.5 mW/cm², 1 h	Cell viability↓, SOD↓, ROS↑, MDA↑
0, 24, 48 h	Human peripheral blood lymphocytes	RPMI-1640	UVA/365 nm, 2.0 mW/cm², 0, 24, 48 h	Cell viability↓, sub-G1 phase↑, caspase-9↑, caspase-3↑, and PARP↑ MMP↓, ROS↑DNA damage↑micronucleus formation↑
4 h	HaCaT	DMEM	UVA/320–390 nm; 0, 2.5, 5.0, and 10 J/cm²	MTS assay (A325, P25 and A25)↓, ROS↑
24 h	HaCaT	MEM	NAC, UVA/NAC: 5 mM, 2 h UVA: 365 nm, 3.5 W/cm², 1 h	Cell viability (UVA)↓ (UVA + NAC)↑, LDH (UVA+NAC)↓, apoptosis assay (UVA + NAC)↓, ROS (UVA + NAC)↓, MMP (UVA + NAC)↑, K6 mRNA (UVA + NAC)↑
12 h	U87-MG	DMEM	UVA/365 nm, 5 J/cm², 20 min	Cell viability↓, BCL2↓, BAX↑
10 min	Leukemia K562	RPMI-1640	Daunorubicin, UVA/daunorubicin: 0.14 mM, 0.2 mM UVA: 100 s	Drug accumulation↑

oxidative stress, oxidative DNA adducts, DNA breaks, and chromosomal damage in L-02 cells. The adsorption of p,p′-DDT by TiO_2 NPs was approximately 0.3 mmol/g. Synergistic genotoxicity induced by a combination of traces of p,p′-DDT and TiO_2 NPs may be a potential environmental risk factor. Sodium fluoride (NaF) and TiO_2 NPs are useful additives in household products such as toothpastes.[3,56] Xie et al[57] examined the combined effects of NaF and TiO_2 NPs (21 nm) in human bronchial epithelial cells (16-HBE) and found that combined exposure of NaF and TiO_2 NPs could enhance the oxidative stress in 16-HBE cells. In another study, Xu et al[58] investigated the interactions of TiO_2 NPs with functional biomolecule lysozymes in culture cells. They found that lysozymes were adsorbed on to the surface of TiO_2 NPs (60 nm) via electrostatic attraction and hydrogen bonds. They therefore suggested that TiO_2 NPs might have some toxic impacts on biomolecules after interacting with biomolecule lysozymes. In summary, studies on the effects of TiO_2 NP interaction with organic or inorganic compounds are limited. The existing evidence indicates that interaction of TiO_2 NPs with BPA, p,p′-DDT, or NaF may result in enhancement of oxidative stress and further cyto or ecotoxicity.

Effects of TiO_2 NP interaction with the physical factor UVA

TiO_2 NPs possess excellent optical and electrical properties.[59–61] Due to photocatalysis, TiO_2 NPs[62,63] are used to degrade formaldehyde and thus improve air quality in the indoor environment. However, some studies suggest that TiO_2 NPs might be toxic under ultraviolet A (UVA), an electromagnetic radiation with wavelength range from 315 nm to 400 nm, ISO-21348. Lu et al[64] found that TiO_2 NPs (20 nm) could induce photocatalytic nitration of the protein tyrosine, which could lead to prevalent post-translational modification by TiO_2 NPs as a result of oxidative and nitrative stress. In another study, Tu et al[65] found that nitrative stress induced by TiO_2 NPs (20 nm) under UVA radiation triggered apoptotic cell death in human keratinocyte cells. This result suggests that skincare products with TiO_2 NP components may cause damage to human keratinocyte cells under UVA radiation. Xue et al[66] investigated the oxidative stress and cytotoxicity induced by different crystalline forms (anatase, rutile, and anatase/rutile) and sizes (4 nm, 10 nm, 21 nm, 25 nm, or 60 nm) of TiO_2 NPs in HaCaT cells under UVA irradiation. They found that TiO_2 NPs could induce ROS generation and toxicity in cells under UVA irradiation. Kang et al[67] also showed that TiO_2 NPs (20 nm) and UVA (0.6 mW/cm^2 for 1 hour) synergistically promoted ROS generation and triggered cell apoptosis. Yin et al[68] examined the phototoxicity of TiO_2 NPs with different sizes and crystal forms (anatase and rutile) in human skin keratinocytes under UVA irradiation. They found that TiO_2 NPs are phototoxic to human skin keratinocytes, and that the phototoxicity is mediated by ROS generated during UVA radiation. Moreover, the phototoxicity of TiO_2 NPs was less with larger particle size and surface areas. Zhang et al[69] investigated the combined effects of TiO_2 NPs and UVA exposure on African clawed frogs (*Xenopus laevis*). They found that, regardless of UVA exposure, the rate of *X. laevis* survival decreased with increased concentrations of TiO_2 NPs. Exposure to 10 nm TiO_2 NPs and UVA significantly decreased the rate of *X. laevis* survival. However, exposure to 32 nm TiO_2 NPs and UVA had no statistical effect on the rate of *X. laevis* survival. This experiment suggests that toxicity is related to the size of TiO_2 NPs to some extent. Bar-Ilan et al[70] also found that TiO_2 NPs under UV produced ROS as the major phototoxic agent to the development of zebrafish. Xue et al[71] examined the chemoprotective effects of N-acetylcysteine (NAC) (5 mM pretreated for 2 hours) on TiO_2 NP-induced (21 nm, 200 μg/mL for 24 hours) oxidative stress and apoptosis in human keratinocytes under UVA (3.5 mW/cm^2 for 1 hour). NAC,[72–74] a nutritional supplement for cysteine donating, is widely used as an antioxidant. They found that NAC could prevent TiO_2 NP-induced oxidative stress and apoptosis in cells. The protective effects of NAC on TiO_2 NP-induced apoptosis were related to modulation of ROS and intracellular nitric oxide levels. It is worth noting that the combined effect of TiO_2 NPs and UVA may be a double-edged sword. Wang et al[75] investigated the antitumor effects of TiO_2 NPs excited with UVA irradiation both in vitro and in vivo. Their results revealed that TiO_2 NPs alone had no effect on glioma cell proliferation. However, when TiO_2 NPs were combined with UVA irradiation, the proliferation rate of cells was decreased significantly compared with controls (TiO_2 NPs alone or UVA alone). They further investigated the in vivo antitumor effects of combined TiO_2 NPs plus UVA on established glioma tumors. TiO_2 NPs plus UVA led to pronounced areas of necrosis, elevated indices of apoptosis, delayed tumor growth, and increased survival compared with the TiO_2 NPs alone or UVA alone. Moreover, the log-rank test for trend in survival analysis of tumors implanted in animals showed that the average survival duration was prolonged. Additionally, degradation, detoxification, and/or bactericidal effects of TiO_2 NPs under UVA to some pesticides or drugs in the ecosystem have been widely investigated.[76,77] Under UV-irradiated conditions

(λ >350 nm), a TiO_2 electron excites an electron from the valance band to the conduction band and electron hole pairs are generated in the surface of TiO_2, which consists of the positive hole (h^+) and electron (e^-). The hole in the valence band has a positive redox potential and is capable of oxidizing organics, H_2O, and hydroxide ions on the surface of TiO_2 NPs, and eventually to generate hydroxyl radicals (OH). At the same time, the electron promoted from the valence band to the conduction band reduces oxygen into a superoxide radical (O_2^-). OH, O_2^-, and other perhydroxyl radicals have a strong oxidability to degradate pesticides, drugs, and organic substances (Figure 2). The photocatalytic effects of TiO_2 NPs have been indicated to degrade pesticides such as endosulfan and organochlorine.[78] Seitz et al[79] found that TiO_2 NPs (~100 nm; 0.2 mg/L) could reduce nearly 30% of the pirimicarb concentration under UV irradiation (40 W/m^2 for 15 minutes), which resulted in an almost complete removal of pirimicarb toxicity to *D. magna*. Zhao et al[80] indicated that TiO_2 NPs under UV irradiation could degrade oxytetracycline, which is widely used in both human and veterinary medicine. Higher degraded toxic byproducts were detected by a standardized bioluminescence assay of inhibition rate on *Vibrio qinghaiensis* sp.–Q67 (Q67), which indicates that a possible enhancement in ecological toxicity may occur after combination of TiO_2 NPs with oxytetracycline under UVA irradiation. These results indicate that the photocatalytic effect of TiO_2 NPs on pesticides and drugs under UVA irradiation may result in either increased or decreased toxicity, depending on the characteristics of the byproducts.

Li et al[81] demonstrated that Ag–TiO_2 NPs showed a greater synergistic bactericidal activity under UV than TiO_2 (inert) or pure Ag NPs alone to Gram-positive bacteria *Bacillus subtilis* and Gram-negative bacteria *Pseudomonas putida* at 25°C. Additionally, Song et al[82] found that the synergistic effect of TiO_2 NPs under UV irradiation could enhance the drug accumulation dose in targeted leukemia K562 cells and inhibit multidrug resistance. Their findings suggest that combined effects of TiO_2 NPs and UVA irradiation may be beneficial for tumor treatment. TiO_2 NPs have been well investigated in recent years for enhancing the photocatalytic activity, coating, and doping of zinc oxide (ZnO) on to its surface.[83,84] Liao et al[83] found that TiO_2/ZnO composite NPs had a higher photocatalytic activity in the degradation of methyl orange than both TiO_2 and shape-controlled NPs alone. Additionally, Jiang et al[85] demonstrated that a combination of the nanosized TiO_2 and ZnO powders displayed high photocatalytic activity toward the decolorization of C.I. Basic Blue 41 in water under solar radiation, and a Ti/Zn molar ratio of 1:1 showed highest photocatalytic activity.

In conclusion, TiO_2 NPs excited with UVA irradiation could induce ROS generation and thus trigger photocatalytic nitration of the protein tyrosine, oxidative stress, and eventually cell apoptosis. Increased oxidative stress damage may be the principal toxic mechanism. Combined toxicity of TiO_2 NPs under UVA may be through ROS-mediated upregulation

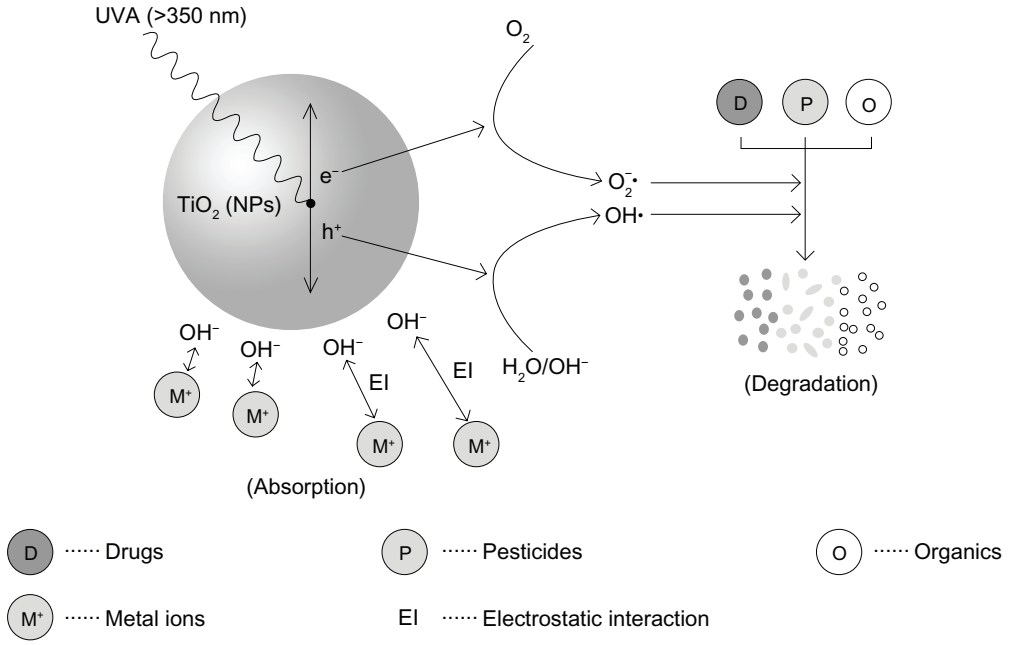

Figure 2 Interactive effects (degradation and absorption) of titanium dioxide (TiO_2) nanoparticles (NPs) with chemicals under ultraviolet A (UVA) radiation.
Abbreviations: OH, hydroxyl radicals; O_2, oxygen; O_{2^-}, superoxide radical; H_2O, water; e^-, electron; h^+, the positive hole.

Table 2 Studies in vivo on the interactive effects of TiO_2 NPs with chemicals or physical factors

Reference	Supplier	Characteristics of TiO_2 NP			Dispersion method	Living organism
		Particle size (nm)	Crystal structure	Surface area (m^2/g)		
20	Zhejiang Hongsheng Nanotechnology	50, 120	NA	NA	Sonicated for 20 min	Kun Ming mice
32	Skyspring Nanomaterials Inc	5–10	NA	NA	Mixed in a shaker for 24 h	*Ceriodaphnia dubia*
35	Nanjing High Technology Material	13.5	Anatase	NA	Sonicated for at least 30 min	*Daphnia magna*
41	Degussa	21	NA	50	NA	*Cyprinus carpio*
42	Evonik Degussa	21	NA	50 ± 15	Pre-equilibrated for at least 24 h	Zebrafish
43	Vivo Nano	1–10	Anatase	NA	Coated with hydrophilic sodium polyacrylate	*Chlamydomonas reinhardtii*
58	Degussa	21	NA	NA	Ultrasonicated for 10 min	*Micrococcus lysodeikticus*
69	Alfa Aesar	5, 10, 32	NA	210, 115, 45	NA	*Xenopus laevis* 0
75	Sigma-Aldrich	NA	Anatase and rutile	NA	Sonicated for 30 min	Female BALB/c nude mice
79	Degussa	21	80% anatase, 20% rutile	50 ± 15	Sonicated for 10 min	*D. magna*
80	Degussa	27	NA	50	Dispersed on 5 A or 13X surface	*Vibrio qinghaiensis* sp.-Q67

Note: [a]The combined effects are effects with TiO_2 NPs and combined factors, comparing with effects of $nTiO_2$ or combined factor alone.
Abbreviations: ↓, inhibit, decrease, suppress, or delay; ↑, increase; ↔, no significant changes; GSH, glutathione; NA, data not available; NPs, nanoparticles; ROS, reactive oxygen species; SOD, superoxide dismutase; T, temperature; TiO_2, titanium dioxide; UVA, ultraviolet A; MDA, malondialdehyde; CD, cadmium; HA, humic acid; NaH_2AsO_4, sodiumarsenate; OTC, oxytetracycline; min, minutes; PbAC, Plumbi Acetatis; h, hours; d, days; pH, the acidity or basicity of an aqueous solution; $nTiO_2$, nano-TiO_2.

of the death receptor Fas, and activation of the preapoptotic protein Bax.[86] Meanwhile, ROS-induced p53-mediated DNA damage can lead to G_2/M cell-cycle arrest or delay and mitochondrial DNA damage.[67,69,88] These procedures can ultimately lead to cell apoptosis. This combined toxicity could be alleviated by antioxidant NAC. The combined effects of TiO_2 NPs and UVA are a double-edged sword. Synergistic effects in ROS generation and cytotoxicity after a combination of TiO_2 NPs and UVA irradiation may be beneficial in the treatment of tumors. A combination of TiO_2 NPs and UVA irradiation may also be helpful in degradation of pesticide or drug content in the environment. The beneficial effects also include enhancement in bactericidal activity. However, degradation may also be a possible contributor. An enhancement in toxicity in the ecosystem occurs when higher toxics are degraded and byproducts are generated. Therefore, more studies are necessary to elucidate the effects of the interaction of TiO_2 NPs with different drugs or pesticides in ecosystems under UV radiation.

Summary

Research data on the effects of the interaction of TiO_2 NPs with chemicals or physical factors are emerging slowly. Experimental factors such as agglomeration/aggregation of NPs, cell type, dispersion method, or culture medium may all affect the experiment results,[15,88–90] which may inevitably cause difficulties in interpreting these results. To give the whole picture of the experiments, we summarize in detail the combined toxicities of TiO_2 and chemicals or physical factors for all available studies in Tables 1 and 2.

The existing evidence suggests that TiO_2 NPs can absorb metals, including Pb, As, Cu, and Cd, or their ions in solution. A combination of TiO_2 NPs with metals, organic or inorganic compounds such as BPA, p,p-DDT, or NaF, and physical factors such as UVA light can result in an increase in oxidative stress and toxicity in culture cells or in aquatic animals. Oxidative stress may further induce tumor gene expression or lead to nuclear and mitochondrial DNA damage in mammalian cells. Further well-designed studies are necessary to

Exposure concentration	Exposure method	Exposure time	Exposure condition of combined factors and experiment	Combined effects[a]
5 g/kg	Oral gavage	7 d	PbAC: 500 mg/kg	Liver and kidney function↓; ROS: liver↑, kidney/cortex/hippocampus↔; MDA↔; liver/kidney: SOD↔, GSH-Px↔, cortex and hippocampus: SOD↓, GSH-Px↓
200 mg/L	In food	24 h	NaH_2AsO_4: 0, 0.45, 0.75, 1.5, 2.25, 2.5, 3, and 4.5 mg/L; pH = 7.8, T = 20°C	TiO_2 NPs concentration: mortality at low dose↑; mortality at high dose↓
2 mg/L	In water	3 d	Copper nitrate: 10, 20, 30, 40, 50, 70 and 100 μg/L; pH = 7.6, T = 23°C	Cu^{2+} LC50↓, metallothionein level↓
10.0 ± 1.3 mg/L	In water	0, 5, 10, 15, 20, 25 d	Cd: 3 4.4 ± 4.8 μg/l, 97.3 ± 6.9 μg/L; pH = 7.8, T = 23°C ± 2°C	Cd accumulation↑
5, 10, 20 mg/L	In water	0, 1, 2, 5, 8, 12, 16, 20 d	HA: 5, 10, 20 mg/L; Cd: 50 μg/L; pH = 7.0, T = 25°C ± 2°C	Uptake rate constants of Cd bioaccumulation: HA/TiO_2↑, HA& TiO_2↓
1, 3, 10, 30, and 100 mg/L	In water	0, 0.25, 0.5, 0.75, 1, 2, 6 h	Cd: 0, 0.1, 0.3, 0.5, 0.8, 1.0, and 3.0 mg/L; pH = 7.5 ± 0.1, T = 25°C	Free Cd^{2+} concentration in media↓
0, 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 80, and 100 mg/L	In water	10 min	Lysozymes: 0, 0.42, 0.97, 1.39, 2.08 μM; pH = 7.4	Bacteriolysis activity of lysozyme↓
31, 1, 3.1, 10, 31, 100, 310, and 1000 mg/L	In water	14 d	UVA: 400 mW/m^2; pH = 7.0~7.8	*X. laevis* survival↓; tadpole: body length↓, development stages↓,
200 μg per tumor	Air pouch	12 h	UVA: 365 nm, 5 J/cm^2, 30 min	Necrosis↑, apoptosis↑, tumor growth↓, survival↑
0.02, 0.2, and 2.0 mg/L	In water	72 h	Pirimicarb: 20 μg/L; UVA: 300–400 nm, 40 ± 5 W/m^2, 15 min; T = 20°C ± 1°C	UVA and nTiO_2: pirimicard concentration↓
1, 5, 10, and 15 wt%	In solution	30, 60, 270 min	OTC: 50 mg/L; UVA: 254 nm, 845 μW/cm^2, 2 h; pH = 7	(TiO_2/5A or TiO_2/13X) and UVA: inhibition rate↑

elucidate possible mechanisms of these combined effects. In addition, combined toxicity of TiO_2 NPs with ZnO/Fe_3O_4 is yet to be investigated by molecular biological and toxicological experiments. Meanwhile, studies on the combined toxicity of TiO_2 NPs with other nanosized particles in toxicology and nanomedicine are also urgently needed. Human epidemiological investigation on the combination of TiO_2 NPs with other chemicals is urgently encouraged because TiO_2 NPs are increasingly being used as drug carriers in nanomedicine. Studies on the combined effects of TiO_2 NPs with chemicals or physical factors on aquatic animals are also urgently needed. In addition, the combined effects of TiO_2 NPs with chemicals or physical factors may serve as a double-edged sword. Therefore, studies are also encouraged for TiO_2 NP application in heavy metal pollution prevention and tumor treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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