



Review

Influence of Titanium Dioxide Nanoparticles on Human Health and the Environment

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Abstract: Nanotechnology has enabled tremendous breakthroughs in the development of materials and, nowadays, is well established in various economic fields. Among the various nanomaterials, TiO₂ nanoparticles (NPs) occupy a special position, as they are distinguished by their high availability, high photocatalytic activity, and favorable price, which make them useful in the production of paints, plastics, paper, cosmetics, food, furniture, etc. In textiles, TiO₂ NPs are widely used in chemical finishing processes to impart various protective functional properties to the fibers for the production of high-tech textile products with high added value. Such applications contribute to the overall consumption of TiO₂ NPs, which gives rise to reasonable considerations about the impact of TiO₂ NPs on human health and the environment, and debates regarding whether the extent of the benefits gained from the use of TiO₂ NPs justifies the potential risks. In this study, different TiO₂ NPs exposure modes are discussed, and their toxicity mechanisms—evaluated in various in vitro and in vivo studies—are briefly described, considering the molecular interactions with human health and the environment. In addition, in the conclusion of this study, the toxicity and biocompatibility of TiO₂ NPs are discussed, along with relevant risk management strategies.



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Keywords: TiO₂; titanium dioxide; human health; environment; toxicity; oxidative stress; biocompatibility; risk management

1. Introduction

TiO₂ is one of the most abundant and widely used metal oxide nanomaterial in the world [1,2]. As an n-type semiconductor, with a band gap energy of 3.2–3.35 eV, depending on its crystal phase, TiO₂ acts as an effective photocatalyst during the photocatalytic process for surface functionalization [3–6]. It has three crystalline structures: anatase, rutile, and brookite. Anatase is the most common type and rutile is the most stable form, while brookite is the rarest [7]. There is also amorphous TiO₂, which is a non-crystalline form. TiO₂ exists in various nanostructures, such as nanoparticles, nanotubes, nanorods and nanowires, nanofilms, nanosheets, and nanocoatings, with remarkable photocatalytic activity, which attract scientists to develop potential technological applications in multidisciplinary fields for industrial production [8].

TiO₂ is widely used in food, paints, plastics, printing inks, papers, and biomedical and cosmetic products. Due to its unique properties, TiO₂ is also advantageously used in textiles. For example, when applied to textile fibers, it confers various functionalities such as UV protection, photocatalytic self-cleaning and antimicrobial activity, electrical conductivity, and antistatic properties, as well as increased thermal stability. Moreover, it can also be used for solar energy conversion in the production of electronic textiles or wearable electronics. However, when tailoring its desired functionality, TiO₂ is usually deposited on the surface of textile fibers, but due to its fairly poor adhesion to the fibers, a certain amount of TiO₂ washes away, peels off, or wears off during the product's lifetime. Therefore, such continuous leaching of TiO₂ into the environment results in a potential threat to human health and the ecosystem.

Extensive use of TiO₂ NPs reasonably raises significant concerns due to their potential nanotoxicity, induced by oxidative stress, which is influenced by ROS (Reactive Oxygen Species) formation on the surface of TiO₂ NPs in the presence of UV light [9–12]. After the penetration of TiO₂ NPs into the human body, inflammation, cytotoxicity, genotoxicity, immunotoxicity, and neurotoxicity may occur. Such nanotoxicity can damage the liver, kidneys, lungs, and skin. Special attention must be paid to production workers, in particular, who are in daily contact with high concentrations of TiO₂ NPs. For instance, it has been proven that TiO₂ NPs smaller than 20 nm cause a higher inflammatory response in human cells [13]. Furthermore, TiO₂ NPs also pose certain damage to end users and researchers and, at lower concentrations, TiO₂ NPs act as immunomodulatory agents, inducing inflammatory responses through specific interactions with immune system cells [14,15].

Undoubtedly, TiO₂ is released into most ecosystems, including in the agricultural field, where its potential effects on soil properties, soil microflora, and plants are yet to be investigated. However, TiO₂'s potential nanotoxicity to the aquatic ecosystem is currently under study, and has thus far revealed that TiO₂ NPs negatively affect the suppression of the immune system of fish and invertebrates. Despite this, more research is needed to address the bioaccumulation profile of TiO₂ and its associated biomagnification in the food web. To date, controversial results have been found when studying the toxicity of TiO₂ NPs, which may be due to different particle sizes, doses, culture media, or test methods used [7,16]. Recently, green nanotechnology has been adopted by researchers to ensure the biocompatible and environmentally friendly use of TiO₂ NPs by overcoming their drawbacks.

Due to the widespread use of TiO₂, exposure to NPs by ingestion, inhalation, or sorption has become virtually inevitable. In the last five years, reviews have been published on the effects of TiO₂ NPs in living organisms, focusing either on the toxicology of TiO₂ NPs [1,2,11,17–23], safety concerns in various applications [24–28] and related impact on human health [28–33], or their effects on water/soil/environmental quality [34–38]. Such review studies are necessary to conclusively determine the environmental and human effects of TiO₂ NPs. The purpose of this paper is to review recent advances in the potential health and environmental effects of TiO₂ NPs in order to contribute to the establishment of a scientific basis for the safe application of TiO₂ NP and to promote the sustainable development of nanotechnology. Accordingly, the main exposure modes of TiO₂ NPs, their potential toxicity mechanisms on human cells through various signaling pathways along with the negotiable toxicity, the health effects of exposure to TiO₂ NPs, the biocompatibility, and the environmental effects of TiO₂ NPs are discussed in detail.

2. Modes of Exposure

2.1. Inhalation

Inhalation is the major route of nanoparticle penetration into the body [33,39]. When TiO₂ NPs are inhaled, they are transported to various lung tissues, capillaries, airways, and alveoli and translocated to the heart, liver, nervous system, etc. [13]. Depending on the duration and concentration of inhalation, TiO₂ NPs undergo short- and/or long-term clearance from bodily compartments. By inhalation, finer particles, such as anatase TiO₂ NPs, have a more toxic effect than the comparatively coarser rutile form [40]. For a short-term, single-cycle inhalation threshold, a value of 3.5 mg/m³ is assumed for spray applications. For repeated inhalation, a threshold of 17 mg/m³ is assumed for an 8-h workday. In reality, however, the actual threshold is likely to be even higher. Nevertheless, it was shown that an inhalation concentration of up to 35 mg/m³ does not lead to chronic pulmonary overload [40].

2.2. Oral Route

TiO₂ NPs can enter the blood via the oral route as they are used in foods, personal care products, sunscreens, and toothpaste. TiO₂ NPs remain in the major organs for a long time and are eventually excreted in the stool. Absorbed TiO₂ NPs in the liver, spleen, kidney,

and lung tissues are responsible for possible nephrotoxicity and liver damage [41]. Even after the prolonged release of NPs, they can affect living organisms in the environment via biological pathways [42].

2.3. Dermal Route

Human skin has unique barrier properties that act against the penetration of TiO₂ NPs into the skin. Several studies have found that TiO₂ NPs cannot penetrate through the human dermis, even when their particle size is smaller than 100 nm [43]. Moreover, other studies have revealed that the TiO₂ NPs that do manage to penetrate the skin do not exhibit toxicity under certain conditions [44].

2.4. Injection

TiO₂ NPs can be developed as a highly efficient photothermal, medicinal, and synergistic agent to repair/remove diseased tissues such as cancer both in vitro and in vivo with negligible toxic properties, tissue damage, and kidney/liver dysfunction [45,46]. After injection of TiO₂ NPs, endothelial cells can be disrupted, and they can proliferate and migrate despite the induction of toxicity and immunogenicity. It has been shown that TiO₂ NPs injected into the blood during photothermal cancer therapy enrich the cancer tissue by diffusing, engulfing the cancer cells, and eventually killing them completely [47–49].

3. Toxicity of TiO₂ NPs

There is a lack of information on the potential toxicity of TiO₂ NPs. Indeed, despite numerous studies in this field, it is difficult to find separate studies using the same TiO₂ NPs with the same experimental protocol to compare the results obtained. Nevertheless, the existing data support the potential toxicity of TiO₂ NPs in humans, model vertebrates and invertebrates, plants, algae, and microorganisms. The mechanism of toxicity of TiO₂ NPs to organisms can be outlined as follows: (i) production of reactive oxygen species (ROS) and formation of electron-hole pairs in the presence of light; (ii) binding of TiO₂ NPs to the cell membrane via electrostatic interactions, resulting in cell wall damage and peroxidation of lipids in the cell membrane; and (iii) binding of TiO₂ NPs to intracellular organelles and biological macromolecules [50].

3.1. Cytotoxicity

It is well known that ROS (i.e., superoxide (O₂^{•−}), hydrogen peroxide (H₂O₂), and the hydroxyl radical (OH[−])) are produced by aerobic organisms within the cell and are normally in equilibrium with antioxidant molecules (Figure 1a) [51]. The imbalance between ROS and antioxidants (AOX) caused by the excessive production of ROS or the depletion of antioxidant molecules leads to the occurrence of oxidative stress (Figure 1b,c) [51].

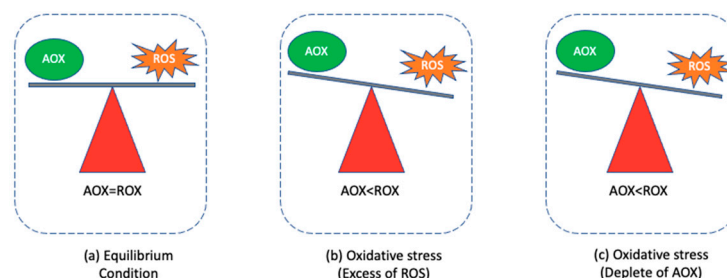


Figure 1. Equilibrium of ROS and antioxidants (AOX) (a) and their disequilibrium causing oxidative stress, either by an excess of ROS (b) or a deficiency of AOX (c).

As for the negative biological effects, oxidative stress is the most important process involved in the formation of TiO₂ NPs-induced ROS [52]. High TiO₂ concentrations cause greater oxidative stress, which correlates with the increase in lipid peroxidation at the cell membrane after TiO₂ NPs adsorption on the cell membrane. TiO₂ NPs-induced ROS

and lipid peroxidation damage the integrity of the cell wall and membrane, resulting in increased permeability [53], which allows TiO_2 NPs to enter the cell. In addition to free diffusion, TiO_2 NPs can also enter the cell through the process of endocytosis. While particles larger than 500 nm can be removed by phagocytes [50], smaller particles can be engulfed by a cell membrane vesicle and taken further into the cell. Accordingly, TiO_2 NPs with a size of 25 nm and less have been taken up into human keratinocytes [54], as well as lung cells [52,55], lymphocytes [56], macrophages [57], keratinocytes [58], and hepatocytes [59] after endocytosis. It is also interesting to note the penetration ability of TiO_2 particles with a size of 200 nm into red blood cells, which were chosen as a model for non-phagocytic cells. The results demonstrated the ability of the particles to penetrate the red blood cell membrane by a mechanism other than phagocytosis and endocytosis [60]. In this case, the penetration mechanism remained unexplained.

Upon entrance of TiO_2 NP into the cell, the internalized TiO_2 NPs are transported to lysosomes, where they generate lysosomal stress and release cytosol that reacts with cellular components, resulting in DNA damage, DNA rearrangement, altered gene expression, oxidative stress, and inflammation (Figure 2) [28,56,61–63]. TiO_2 NPs impair micromolecular functions by protein adsorption, blocking signaling pathways, and binding to DNA structure [64,65]. Undoubtedly, such damage affects cell viability [66] and is dose and time dependent [67,68].

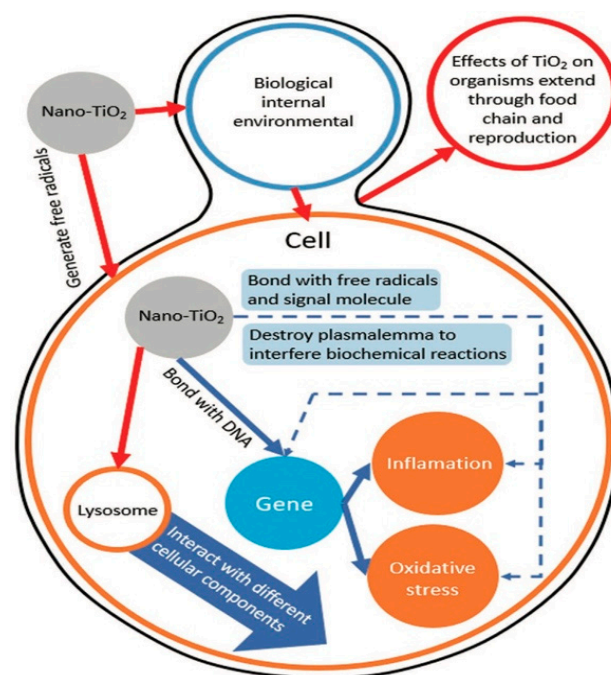


Figure 2. Toxicity mechanism of the reaction of TiO_2 NPs with cells. Adapted with permission from [28]. Copyright, 2020 John Wiley & Sons, Inc.

It should also be noted that the response of cells in the presence of TiO_2 NPs is complex. Thus, the presence of TiO_2 NPs can modulate different cell fates, including necrosis and apoptosis, which are regular cell death pathways, or autophagy, which leads to either cytoprotective mechanisms or cell death (Figure 3) [69]. TiO_2 NP-induced autophagy can be exploited in new therapeutic pathway treatment of various diseases (see Section 6).

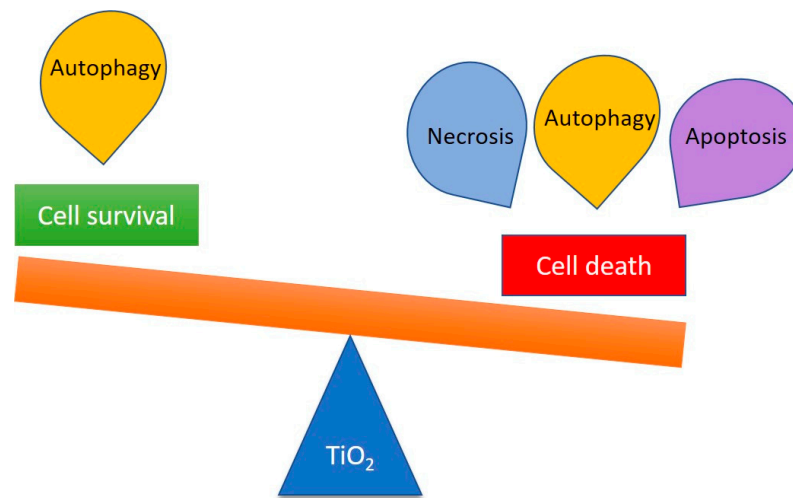


Figure 3. Influence of TiO₂ NPs on the cell fate.

3.2. Genotoxicity

The genotoxicity of TiO₂ NPs has not yet been clarified as scientists do not have sufficient evidence of genotoxicity [70,71]. Genotoxicity refers to the ability of TiO₂ NPs to disrupt genetic information by causing breaks, lesions, deletions, mis-segregation, or non-disjunction in the DNA, leading to gene mutations. In vitro testing methods, such as mammalian chromosomal aberration tests, cellular gene mutation tests and bacterial reverse mutation tests, are performed to measure genotoxicity [72,73]. In contrast, the in vivo comet assay and the in vivo micronuclei/chromosome aberration assay evaluate in vivo genotoxicity [74]. The genotoxic effect of TiO₂ NPs on cells is mainly studied through the circulatory or respiratory system. Despite the crystallinity of TiO₂ NPs, their genotoxicity mostly depends on their particle size. Smaller TiO₂ NPs possess a stronger genotoxic effect than larger ones, as they easily penetrate into the nucleus and cytoplasm of the cell [74]. Larger agglomerations of TiO₂ NPs cause DNA damage [75]. Several studies have shown the genotoxic and cytotoxic effects of TiO₂ NPs on human amniotic epithelial cells [76], human lung fibroblasts [77], human lymphocytes [78], and human hepatoma HepG2 cells [79]. In vitro studies of cell-induced genotoxicity caused by TiO₂ NPs due to DNA breakage and gene mutations are shown in Figure 4 [22].

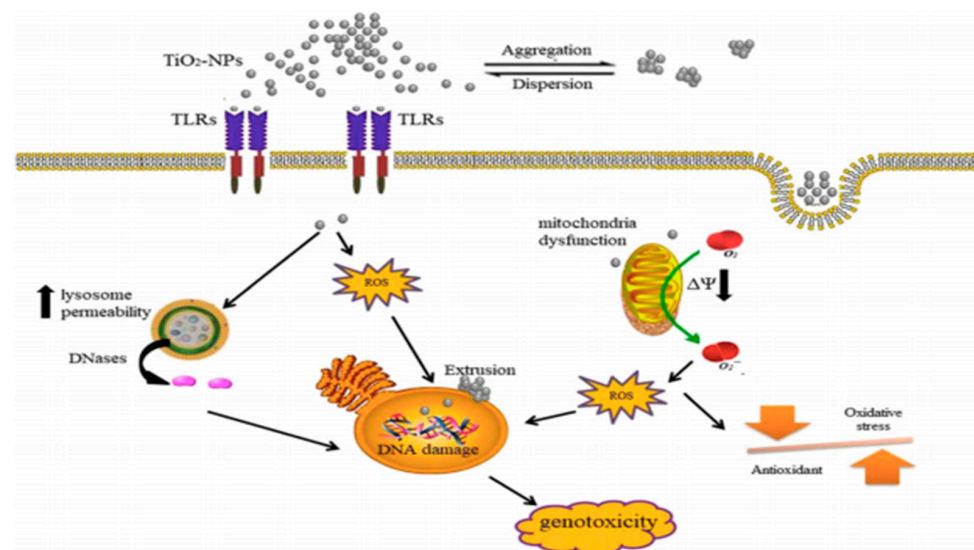


Figure 4. Mechanism of possible genotoxicity of TiO₂ NPs in cells. Adapted with permission from [22]. Copyright, 2021 Springer Nature.

Genotoxicity occurs via direct or indirect genotoxicity mechanisms. Namely, TiO₂ NPs can enter the nucleus, inducing direct DNA damage through direct contact with DNA and chromosome, while indirect genotoxicity of TiO₂ NPs results from the increased lysosomal release of DNases, the formation of nanoaggregates that can extrude nucleus or by ROS accumulation. Moreover, TiO₂ NPs can also negatively influence the repair process of DNA. In vitro studies showed the genotoxicity of TiO₂ NPs during short-term exposure, which may be triggered by smaller particle sizes and mixed phases of TiO₂ NPs [22].

Research has provided contradictory results regarding TiO₂ NPs' genotoxicity [7,80]. Several studies found TiO₂ NPs to have no genotoxic effect [7,57,80,81]. Brandão et al. examined TiO₂ NP-induced genotoxicity in human lung, liver, glial, and neuron cells [82]. They found no genotoxicity, while TiO₂ NPs were successfully internalized by the experimental cells.

4. Health Effects of Exposure to TiO₂ NPs

4.1. Immune System

The immune system defends the body against foreign antigens. If nanoparticles are recognized as foreign substances, they are eliminated by the immune system. If, on the other hand, the foreign substances are not recognized as a threat, they are either ignored or tolerated by the immune system [83]. The effects of TiO₂ NPs on immune function are poorly documented. Underlying molecular mechanism by which TiO₂ NPs influence the immune cell was studied in relation to TLRs, which are a subfamily of pattern recognition receptors, placed strategically on the cell surface and endosome of primary immune cell macrophages [84]. TiO₂-induced immunotoxicity was proven, which occurred through the activation of several receptors, which further activated specific signaling pathways to reduce the antioxidants through the formation of ROS. Upon increased ROS exposure, the mitochondrial membrane potential ($\Delta\psi_m$) reduced, ultimately leading to apoptotic cell death, and inducing immunotoxicity through immune redox imbalance (Figure 5). However, in vivo experiments are essential to further validate TiO₂ NPs influence on the immune system.

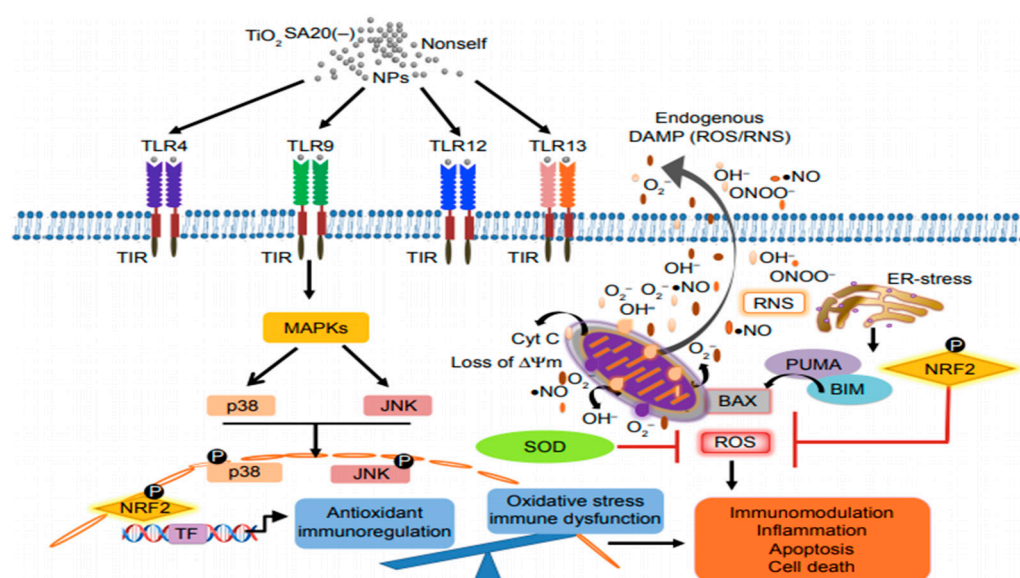


Figure 5. Mechanism of TiO₂ NP-induced immunotoxicity in cells (TLR = Toll-like receptor; MAPK = mitogen-associated protein kinase; JNK = c-jun N-terminal kinase; NRF2 = nuclear factor erythroid 2 factor 2; and SOD = super oxide dismutase). Adapted with permission from [84]. Copyright, 2018 Dove Medical Press Limited.

4.2. Neural System

TiO₂ NPs can enter the brain regions by translocation across the blood–brain barrier or thenose–brain barrier, and progeny across the placental barrier, which may be the reason for the dysfunction and potential risks to the central nervous system [32,85–87]. Long-term exposure to TiO₂ NPs can cause damages to the neurons and glial cells (U373), which may subsequently lead to neurotoxicity [32,88], also at low doses. In Figure 6, it is shown that the oral ingestion of TiO₂ NPs can affect brain activities via increased oxidative stress, decreased antioxidant enzyme activity, and increased nitric oxide (NO) and ROS release (Figure 6) [89]. TiO₂ NPs thus induced a neurotoxic damage accompanied by the increase in degenerated and apoptotic neurons in cerebral cortex.

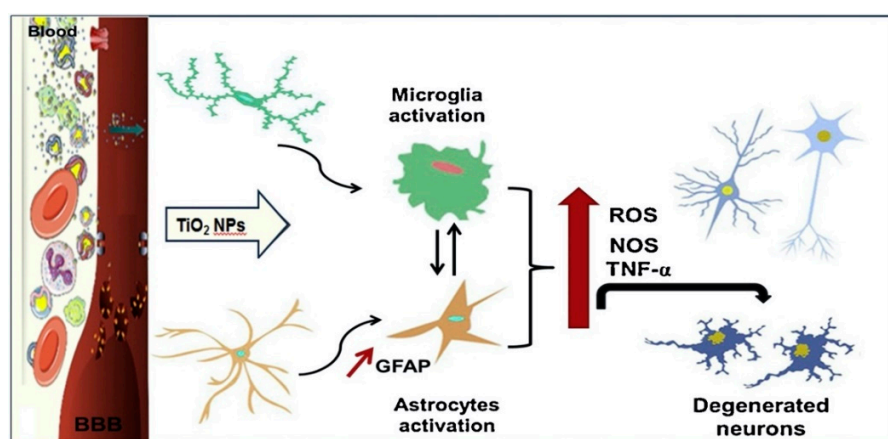


Figure 6. Mechanism of neurotoxicity of TiO₂ NPs in cells. Adapted with permission from [89]. Copyright, 2020 Elsevier B.V.

4.3. Cardiovascular System

TiO₂ NPs of 100 nm significantly reduce mitochondrial ‘dehydrogenase activity’ in human lymphocyte cells [81]. Mitochondria-mediated apoptosis-based cell death due to DNA damage is induced by TiO₂ NPs. When TiO₂ NPs react with hemoglobin, they can weaken red blood cell oxygen transport. Kongseng et al. investigated the cytotoxic effects of TiO₂ NPs on human blood cells, namely peripheral blood mononuclear cells (PBMCs). TiO₂ NPs incubated for 24 h significantly suppressed cell viability and increased the formation of toxic mediators (Figure 7) [10]. At high TiO₂ NP concentrations ($\geq 25 \mu\text{g mL}^{-1}$), cell apoptosis and the ‘proinflammatory cytokine secretion’ of PBMCs increased due to oxidative stress caused by ROS. The effect of TiO₂ NPs and bulk material in PBMCs, neopterin formation and tryptophan degradation was studied by Becker et al. [90]. Neopterin production was increased in both unstimulated and stimulated PBMCs, while tryptophan breakdown was suppressed, thus suggesting that the total effect of TiO₂ NPs was strongly pro-inflammatory. Namely, in human body fluids, such response is detected in diseases such as infections and cancer, and is also parallel to the course of atherogenesis and neurodegeneration [90].

In contrast, no significant DNA damage caused to human peripheral blood lymphocytes treated with TiO₂ NPs was observed by an alkaline assay. Only extremely higher concentrations (100 μg) can show the genotoxicity of TiO₂ [91].

Very little research has been completed on the effect of TiO₂ NPs on the cardiovascular system. Researchers suspect that deposited TiO₂ NPs in the heart may lead to inflammatory responses, system malfunction, and cardiac damage. Depending on the type and duration of exposure, ultrafine TiO₂ NPs could lead to an increase in heart rate, blood pressure, and cardiac muscle damage [32].

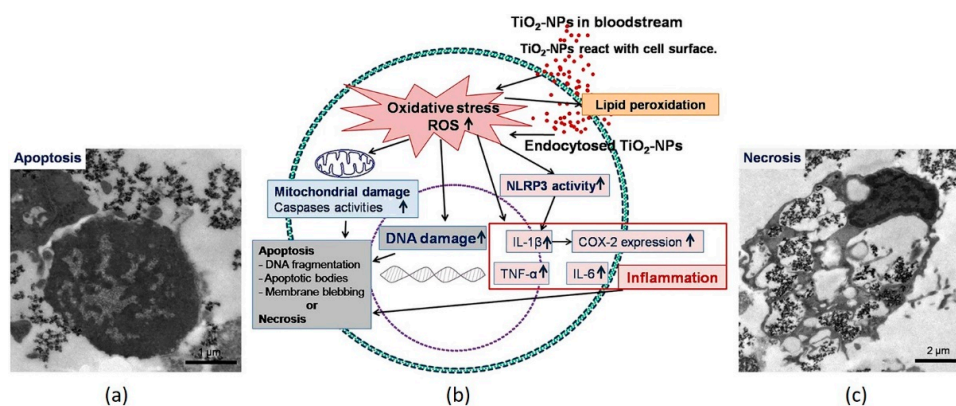


Figure 7. Cytotoxic mechanisms of peripheral blood mononuclear cells (PBMCs) investigated with TiO₂ NPs (b). TEM images of apoptosis (a) and necrosis (c) of PBMCs. (COX-2 = cyclooxygenase-2; IL = interleukin; and TNF = tumor necrosis factor). Adapted with permission from [10]. Copyright, 2016 John Wiley & Sons, Inc.

4.4. Respiratory System

The lungs are the main target system of environmental air pollution via TiO₂ NPs [92]. TiO₂-induced human lung epithelial cell injury (A549) and alveolar lung inflammation have been reported after inhalation in several studies [93–95]. These phenomena lead to lung dysfunction, as well as irreversible changes to the cells, resulting in fibrosis and tumor development. The lung toxicity and inflammatory effects are related to the properties of TiO₂ NPs, such as their size, shape, crystallinity, agglomeration, and surface coating mode [96]. At this point it should be noted that the cytotoxicity of TiO₂ NPs increased in the following order: amorphous > anatase > anatase/rutile; thus, amorphous TiO₂ NPs possessed greater toxic effect than anatase/rutile TiO₂ NPs [95]. Fresegna et al. studied the cellular responses of human alveolar A549 and bronchial BEAS-2B cells to measure the cytotoxic and inflammatory effects of TiO₂ NPs in anatase and rutile forms [7]. They found that anatase TiO₂ NPs exerted greater cytotoxicity on bronchial cells compared to rutile TiO₂ NPs. On the other hand, a higher level of genotoxicity was observed on alveolar and bronchial cells treated with rutile TiO₂ compared to anatase TiO₂. When TiO₂ NPs are pre-irradiated, they have a greater cytotoxic effect on human lung cells compared to non-irradiated TiO₂ NPs [93].

4.5. Digestive System

Oral ingestion of TiO₂ NPs causes them to enter the digestive system. The blood passes through the stomach and also passes through the liver. Significant concentrations of TiO₂ NPs can lead to liver dysfunction, liver cell damage and even liver failure, hepatocyte dysfunction, superficial staining of cytoplasm, and osteoporosis after repeated exposure [40,92]. However, these results, carried out in mice or rats, are controversial, as no toxicity was observed in other studies.

4.6. Urinary System

The kidneys are one of the major organs that filter the blood, remove metabolic wastes, control the body's extracellular fluid balance and electrolyte composition, and return the purified blood to the body. Chen et al. demonstrated an association between TiO₂ NPs and kidney toxicity, suggesting that the kidney may be a major target or organ of exposure to nano-TiO₂ via various routes into the body [92]. When cultured embryonic kidney cells were incubated with TiO₂ NPs, no significant induction of DNA damage was observed. In this case, only the highest concentration of TiO₂ NPs, equivalent to 100 µg/mL, elicited a significant genotoxic response, but it was concluded that such a high concentration of TiO₂ is not environmentally relevant [91]. However, further studies on renal toxicity in humans due to exposure to TiO₂ NPs need to be conducted.

4.7. Reproductive System

Based on the research conducted to date, the toxicity of TiO₂ NPs to the reproductive system such as testes, ovaries, placenta, and fetal tissues in humans is unknown. TiO₂ NPs cause adverse effects on hatching and affect reproduction in zebrafish, as well as pregnancy difficulties such as nanoparticle spread to fetal brain, fetal liver, and placenta in mice [13]. However, the research data are not sufficient to conclude the development of toxicity in the reproductive system of mammals, especially humans.

4.8. Dermal System

The penetration of TiO₂ NPs through human skin has not been found in most studies [97–99]. TiO₂ NPs do not cause ROS formation, cellular glutathione content, nor apoptosis when applied to human epidermal (A431) and keratinocytic (HaCaT) skin cells [100,101]. TiO₂ NPs cause dermal toxicity only when they pass through healthy or damaged skin after long-term exposure [40]. However, the opposite phenomenon has been observed in several studies. Wright et al. showed that TiO₂ NPs induce superoxide formation, caspase, and cell apoptosis in human keratinocyte cells (HaCaTs) in a dose-dependent manner. This causes cytotoxicity in HaCaT cells at 10^{−4}–10^{−5} mol/L [100]. In fact, human skin is not only exposed to TiO₂ NPs, but also external chemicals or stressors, such as UV light [102], which also damage human dermal fibroblasts. The Scientific Committee on Consumer Safety (SCCS) therefore suggested that TiO₂ NPs should not be used in sunscreen formulations with high photocatalytic activity [1].

5. TiO₂ NPs in the Environment (Ecotoxicity)

Ecotoxicity occurs when biological, physical, and chemical stressors affect living organisms in the ecosystem through altered biochemistry, physiology, and cellular interactions. The ecotoxic adverse effects of TiO₂ NPs have been observed in water, aquatic animals, zebrafish gills, food, and aquatic environments [67]. TiO₂ NPs influence the bacterial colonies in soil, reducing microbial biomass and diversity, thereby having a negative effect by changing the bacterial composition of the ecosystem [103,104]. In addition, terrestrial plants collect TiO₂ NPs from the soil and store them in stems, leaves, and fruits, which promotes germination and root expansion [105,106].

5.1. TiO₂ NPs in the Plant and Soil Environment

After the use of TiO₂ NPs in various products, this inorganic nanomaterial is mostly abandoned, and a large quantity of TiO₂ NPs is distributed to the environment, reaching the air, soil, water, and living organisms [54]. Figure 8 represents the use, release pathways, distribution, and interaction of TiO₂ NPs to plants and the surrounding environment. TiO₂ NPs used in pigments, food additives, and personal care products are released into the soil (13.8%), water (18.5%), and air (2.2%). Therefore, plants come into direct contact with TiO₂ NPs through the soil, water, and air.

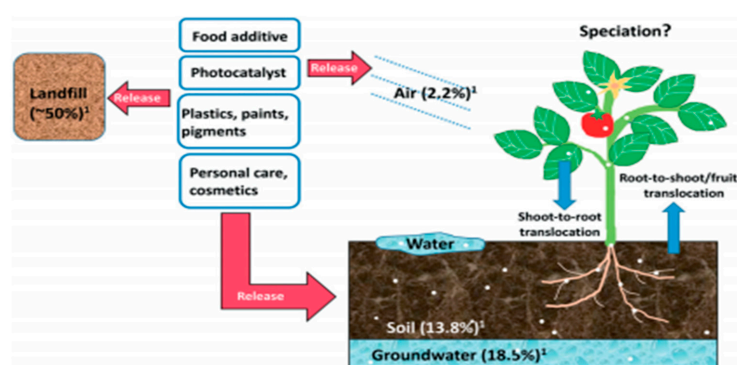


Figure 8. Uses and dispersion of TiO₂ NPs into the environment and interaction with plants. Adapted with permission from [107]. Copyright, 2018 The Royal Society of Chemistry.

After the entry of TiO₂ NPs via several pathways, soil properties—such as soil enzymes, microbial communities, nutritional elements, and pH—affect their behavior, mobility, and bioavailability, thereby determining the fate of TiO₂ NPs. The interconnected soil properties/factors, such as soil type, pH, ionic strength, and organic matter, affect the transport of TiO₂ NPs by changing their zeta potential, aggregation, surface charge, and van der Waals force [108,109]. The existence of microbes in the soil is vitally important for the decomposition and recycling of organic material. As a result, TiO₂ NPs may alter the microbial population, diversity, and activity by changing the soil properties [103,110]. Low concentrations of TiO₂ NPs also increase urea activity [111]. On the other hand, at extremely higher concentrations (1000 mg/L), TiO₂ NPs decrease urea activity [112,113], affect the level of bacterial nitrogen, and reduce catalase, phosphatase, invertase, and peroxidase activities [103]. Reports suggest that TiO₂ NPs also disrupt the gene expression of bacteria, resulting in decreasing nitrogen fixation and methane oxidation, which are essential for the decomposition of proteins and organic pollutants [81].

The interaction between plants and TiO₂ NPs depends on their particle size, crystal phase, and surface coating [107]. Smaller TiO₂ NPs (less than 30 nm) can enter into plant cells by reducing the size of the pores and the flow of water in corn [114] and wheat [115]. Investigations show that TiO₂ NPs of 12, 22, and 25 nm can be translocated from the roots to the leaves [115]. The antioxidant stress is interrupted by TiO₂ NPs in duckweed [116] and tomato [117]. TiO₂ NPs also interrupt different parameters in raceme elm [118], onion [119], soybean [120], rice, spinach [121], and parsley [122]. As TiO₂ NPs show photocatalytic activity under light irradiation, they can alter photosynthesis, metabolism, and gene expression within plants. Some investigations reported negative effects caused by TiO₂ NPs on plant growth, whereas it was concluded that TiO₂ NPs may cause some sensitive plant growth-promoting bacteria to disappear from soil. Accordingly, such impairment of the soil bacterial community composition may further affect ecosystem functioning [123,124].

5.2. TiO₂ NPs in the Aquatic Environment

The significantly increased leakage of TiO₂ NPs into surface and marine water environments has a great impact on aquatic ecosystems. The related studies have been mainly concentrated in determining the behavior of TiO₂ NP in marine environments, focusing mostly on marine plankton and benthos, with comparable contribution of papers, i.e., 42.1% and 44.7%, respectively, as well as in marine fish, with the smallest share of the research, i.e., 13.2% [125]. As TiO₂ NPs are very reactive, they follow different transformation processes when they are released into the aquatic ecosystem. These transformation processes involve physical (agglomeration, aggregation, and sedimentation) interactions with TiO₂ (adsorption), chemical (photochemical) interactions, and biological (biomodification) interactions. The ability of TiO₂ NPs to enter in the aquatic organisms is worrying, as it leads to bioaccumulation in their cellular tissue. Accordingly, NPs negatively affect environmental food webs in three different major ecosystems—freshwater, marine, and terrestrial [24,126]. Bearing in mind that mammals are at the top of the ecological food chain, the ecotoxicity induced by TiO₂ NPs in the environment is easily converted into cytotoxicity in humans (Figure 9) [24].

Phytoplankton is the most dominant factor in marine ecosystems and the food web [127]. The interaction of TiO₂ NPs with marine phytoplankton has therefore been investigated [127,128]. In an aquatic environment, TiO₂ NPs may be adsorbed or diffused by the phytoplankton surface. TiO₂ NP-mediated ROS may be diffused by the cell wall when the TiO₂-plankton complex generates 'ligand-to-metal charge transfer reactions' [126]. After the aggregation and settling of TiO₂ in marine environments, there is still a small fraction of TiO₂ NP nanoparticles in the water column that may be hazardous to the living organisms in that water column. Thus, at higher TiO₂ concentrations (>/20 mg/L), TiO₂ NPs can significantly reduce *P. tricornutum* growth, one of the most widely used model organisms used in marine ecotoxicology studies [127]. Miller et al. demonstrated that, at low UV

levels, TiO₂ NPs' photocatalytic activity can induce toxicity in marine phytoplankton [128]. However, in the absence of UV light, no effects were observed.

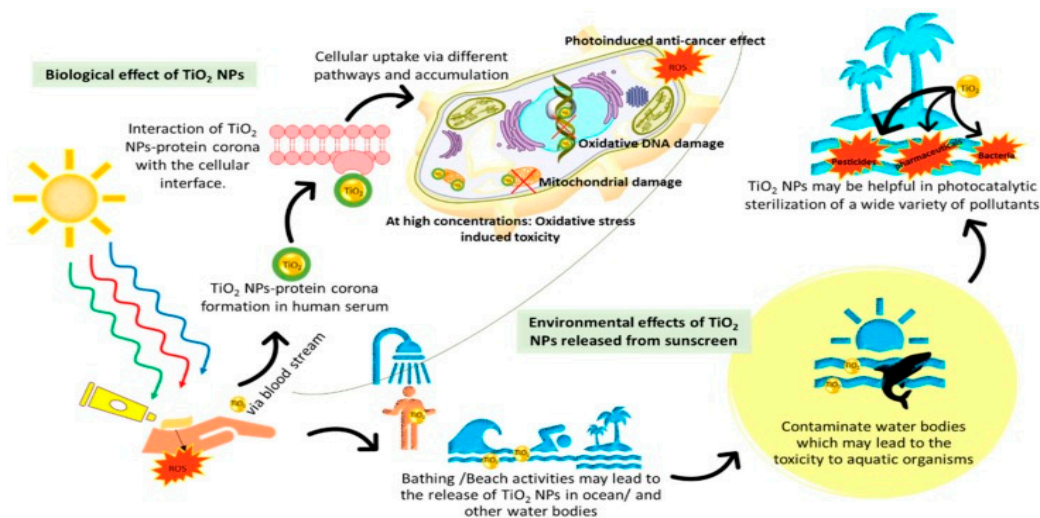


Figure 9. Environmental and biological effects of the TiO₂ NPs. Adapted with permission from [24]. Copyright, 2019 MDPI AG.

The toxicity of TiO₂ NPs in marine mussels has been investigated in several studies [38,129–134]. Due to the filtrating behavior and bioaccumulation tendency of bivalve mollusks, they accumulate various pollutants, such as microalgae, sediments, bacteria, and contaminants, within their tissues [38]. However, no acute TiO₂ NP toxicity was found in marine abalone at TiO₂ NP concentrations from 0.1 to 10.0 mg/L [135]. In spite of the absence of toxicity, minor oxidative stress was induced. In another study, the combined effect of TiO₂ NPs and ocean acidification was assessed in mussels [136]. A low pH increases the toxicity of TiO₂ NPs and the impairment of feeding and metabolism was observed in mussels at different pH and concentrations.

In a different study, the TiO₂ NP–fish interaction was examined at different TiO₂ NP concentrations and exposure conditions [137]. TiO₂ NPs of 0, 1, 10, and 100 mg/L were applied to fish for 96 h, resulting in no mortality or sublethal effects. Very few studies associated with TiO₂ NPs have been conducted on fish. As such, more studies need to be conducted in order to understand the potentially cytotoxic effects of TiO₂ NPs on fish.

Moreover, in aquatic environments, TiO₂ NPs can interact with heavy metals (Cu, Zn, Cd, As, etc.) and toxic organics, resulting in the formation of a harmful environment that can alter the bioavailability of aquatic organisms [38,138,139]. If TiO₂ NPs are exposed to arsenic (As), this can increase arsenic accumulation in aquatic animals and the human food web [139]. However, TiO₂ NP–Cd interactions do not result in toxicity in Mediterranean mussels [140]. The immunotoxicity, genotoxicity, and neurotoxicity of TiO₂ NPs in marine living organisms were reported by several researchers, with varying results depending on the particle size, exposure duration, exposure type, and stress factors [38,134,141–145].

6. Biocompatibility of TiO₂ NPs

The potential toxicity of the TiO₂ NPs discussed above does not suggest that they are unsafe for humans or the environment. Depending on the size and shape of the nanoparticles, TiO₂ NPs may be safe, due to their very low toxicity. When it comes to the issue of skin permeation, long-term skin exposure to TiO₂ NPs can be harmful to humans if they overdose, which is almost impossible in everyday life [146]. Biocompatibility refers to the testing of TiO₂ NPs for cytotoxicity, genotoxicity, immunotoxicity, systemic toxicity, hemocompatibility, pyrogenicity, and implantation, evaluated by ISO, ISO/TR 10993-22:2017 via *in vitro* and *in vivo* studies [47]. The evaluation of the toxicity and biocompatibility of

TiO₂ NPs is crucial to understanding the deleterious biological responses of the properties of TiO₂ NPs, their functionalities, and their contact surfaces (Figure 10a).

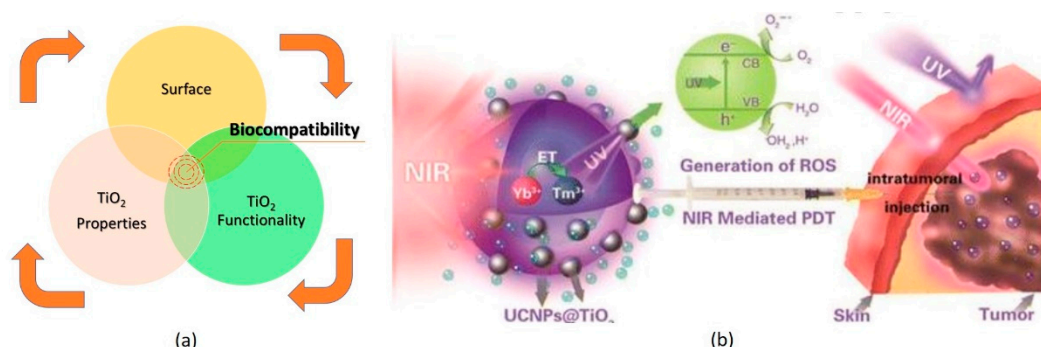


Figure 10. Biocompatibility of TiO₂ NPs (a) and antitumor treatment by TiO₂ NP ROS formation (b). Adapted with permission from [147]. Copyright, 2015 American Chemical Society.

In terms of the biocompatibility of TiO₂ NPs, they are used in drug carrier biosensing, implants, and antibacterial activity [148]. Due to the spherical shape of TiO₂, TiO₂-cell interactions, TiO₂'s biocompatibility, excellent drug release properties, and lower toxicity (than Al₂O₃ and SiO₂) [148–150], TiO₂ NPs are used in antitumor treatments (Figure 10b). Due to the cytotoxic ROS (O₂⁻, OH[•], H₂O₂)-based interaction between TiO₂ NPs and specific cancer cell membranes, surface-functionalized biocompatible TiO₂ NPs have recently been used for targeted cancer therapy [48]. TiO₂ NPs have also been used in the biomedical field in photothermal therapy (PTT), photodynamic therapy (PDT), and sonodynamic therapy (SDT) for cancer treatment via the targeted, controlled, stimulus-driven delivery and release of cytotoxic anti-cancer agents [148]. Due to their low phototoxicity, biocompatibility and stable structure, TiO₂ NPs have potential applications in phototherapy for the treatment of cancer cells [49,151]. When TiO₂ NPs are exposed to light, an oxidative radical (ROS) is generated, which subsequently destroys the cell and cellular components, such as the lipids, proteins, carbohydrates, and nucleic acids in cancer cells [147,152].

Furthermore, several authors have reported that the toxicity of TiO₂ NPs arises due to a 'particle effect' rather than a 'chemical effect' [40]. However, further studies are required to assess the nature, mechanisms, and effects of the toxicity of TiO₂ NPs on humans and the surrounding environment.

7. Risk Management

7.1. Risk Following Oral Exposure

Considering the published studies, TiO₂ NPs have no acute toxic effects after oral exposure. There are insufficient data on the repeated-dose toxicity of TiO₂ NPs, so there is not believed to be any significant risk from oral exposure.

7.2. Risk Following Dermal Exposure

Based on the current data, short-term dermal exposure to TiO₂ NPs has very little or no toxic effect on healthy skin. Further studies on long-term dermal exposure, as well as on damaged skin, are required in order to evaluate TiO₂ NPs' nanotoxicity on the skin [40].

7.3. Risk Following Inhalation

It is well established that smaller TiO₂ NPs are more toxic than comparatively coarser TiO₂ NPs. Anatase TiO₂ is more toxic than rutile TiO₂, with its crystalline structure. In terms of inhalation, particle size, surface area, crystalline structure, agglomeration, and exposure, time plays a crucial role in the toxicity of TiO₂ NPs. Inhalation is a major problem in workplaces due to high concentrations of TiO₂ NPs, as well as the fact that TiO₂ NPs enter the body mainly through respiration.

The establishment of risk management strategies is therefore crucial (Figure 11), particularly in relation to short-/long-term exposure, as well as the frequency and level of exposure; however, such strategies have not yet been developed. Regulations and legalization for controlling TiO₂ NPs and other engineered NPs (ENPs) are unsure, living the interpretation of the scientific data challenging to the government, agencies, industry, and consumers. Recently, suggestions for the safe handling of TiO₂ NPs and other engineered NPs (ENPs) were proposed by Besha et al. [153], highlighting the mitigation approaches to curtail the possible hazard effects of ENPs.

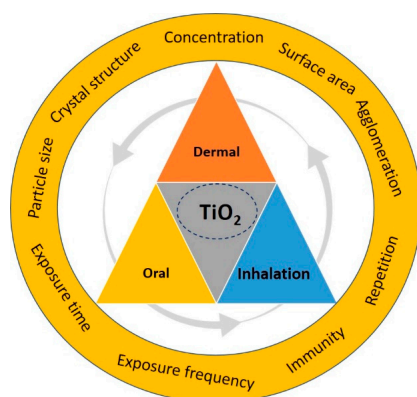


Figure 11. Risk management strategies for human exposure to TiO₂ NPs via different exposure routes.

8. Conclusions and Future of TiO₂ NPs in Textile Applications

TiO₂ NPs are important photocatalysts that are implemented in various fields of application. The toxicity of TiO₂ NPs to human health and the environment is still controversial. TiO₂ NPs are classified as possibly carcinogenic to humans by the International Agency for Research on Cancer (IARC), and as a chemical risk to humans by the Workplace Hazardous Materials Information System (WHMIS) (in group D2A). At lower TiO₂ NP concentrations, recent studies have found that TiO₂ NPs are almost non-toxic, as no remarkable toxicity was observed [99,154,155]. However, TiO₂/textile composites, for example, distinguished by remarkable functional properties [156], have no adverse effects on human skin, as superoxide and hydroxyl radicals are not able to damage human cells from the outside as they cannot enter the inner layer of the human skin [155,157]. As TiO₂/rGO-coated cotton fabric is biocompatible, it does not cause cell membrane damage and cell proliferation, as textiles coated with TiO₂ NPs do not exhibit cytotoxicity over 24 h of incubation [158]. With the exception of the other previously mentioned study, to the best of our current knowledge, no experiments have been conducted with TiO₂ NP-modified textiles on human skin. Considering the toxicity and ecotoxic pathways described in *in vivo* and *in vitro* studies, TiO₂ NPs are the safer option when compared to other metal oxide nanomaterials [148]. The nanotoxicity and contradictive biocompatibility of TiO₂ NPs should be further investigated by researchers, whereas studies on long-term or accelerated effects of TiO₂ need to be carried out in order to estimate precise implications of TiO₂ NPs for human health and the surrounding environment. Therefore, careful consideration should be given to the benefits of TiO₂, and the associated potential risks based on its intended use. Moreover, mitigating the toxicity of TiO₂ NPs transferred from consumer products to the environment requires appropriate strategies and regulatory frameworks to protect humans and the environment. Accordingly, the establishment of international standard methods for the exact evaluation of risk–benefit assessments is a prerequisite to allowing the safe use of TiO₂-functionalized materials.

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