An overview: Neurotoxicity of Titanium Dioxide Nanoparticles induced cognitive impairment in adult zebra fish by focusing on Nrf-2 and Ho-1 signaling

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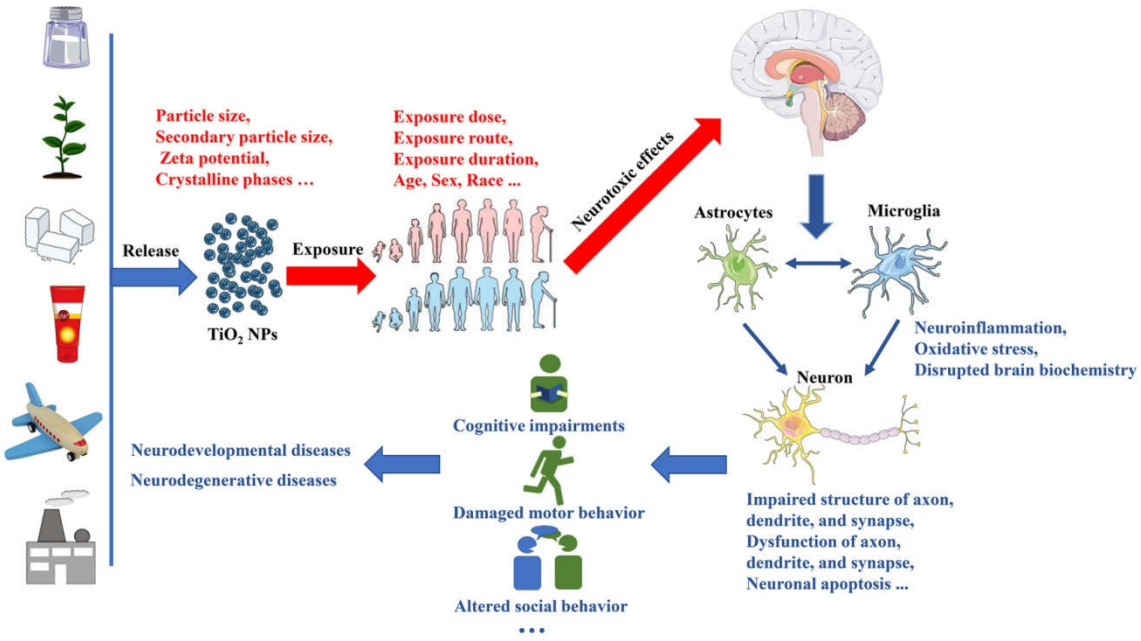
Abstract:

The growing use of titanium dioxide nanoparticles (TiO2 NPs) across miscellaneous fields has surpassed to a growing concern concerning their referring to practices or policies that do not negatively affect the environment adulteration and certain human uncovering. Consequently, significant research works have existed in the direction of understanding the belongings of TiO2NPs on both persons and the surroundings. Notably, TiO2 NPs uncovering has happened guide multiple degradations of the central nervous system. This review aims to determine a survey of the recorded neurotoxic effects of TiO2 NPs indifferent class and artificial models. Following uncovering, TiO2 NPs can reach the mind, although the particular machine and length of atoms that cross the blood-mind obstacle (BBB) wait hazy. Exposure to TiO2 NPs has existed shown to encourage oxidative stress, advance Neuroinflammation, upset intelligence biochemistry, and eventually impair neuronal function and makeup. Subsequent neuronal damage can enhance miscellaneous concerned with manner of behaving disorders and play a significant function in the attack and progress of neuro developmental or neurodegenerative afflictions. Moreover, the neurotoxic potential of TiO2NPs can be affected by miscellaneous determinants, containing uncovering characteristics and the physicochemical characteristics of the TiO2 NPs. However, a orderly corresponding of the neurotoxic belongings of TiO2 NPs accompanying different traits under miscellaneous uncovering environments is still wanting. Additionally, our understanding of the underlying neurotoxic methods applied by TiO2 NPs debris wanting and fragmented. Given these information break, it is authoritative to further search the neurotoxic hazards and risks guide exposure to TiO2 NPs.

Keywords: TiO2 NPs, neurotoxic belongings, oxidative stress, neuronal damage, neurotoxic systems.



1. Introduction

Nano-materials (NMs) are fabrics outlined as bearing at least individual measure varying from 1 to 100 nanometers (nm). Titanium dioxide nanoparticles (TiO2 NPs) rank between the top five NMs used in services crop, in the way that bread additives, toys, cosmetic, photoelectric commodity, and pharmaceuticals (Figure 1).[1,2] Consequently, the attendance of TiO2 NPs in air, water, soil, and other incidental television has evenly raised due to their extensive use.[3] This increasing request and adulteration have fashioned human and animal exposure to TiO2 NPs certain. Apart from skin uncovering, breathing, and spoken exposure, additional routes of uncovering to TiO2 NPs contain intraperitoneal dose, subcutaneous injection, and subcutaneous injection.4 Importantly, however the route of uncovering, TiO2 NPs can eventually enter the fundamental distribution and translocate to differing tissues and tools (Figure 2).[4] As the accumulation of TiO2 NPs in the material increases, the mixed well being hazards enhance more severe.[5]

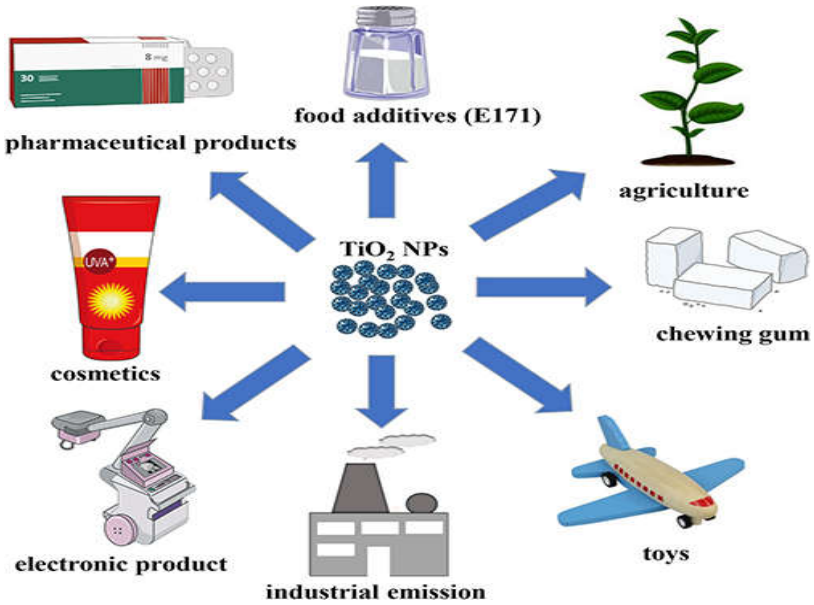


Figure 1 **Application of TiO_2 NPs**

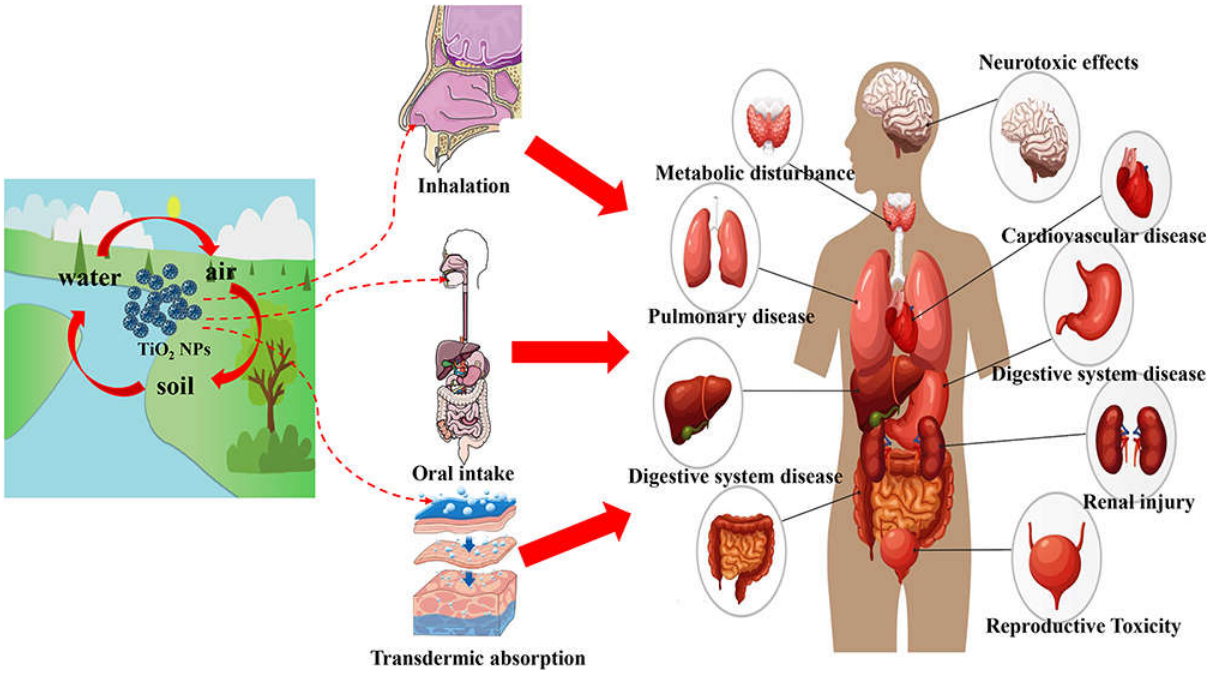


Figure 2 **TiO_2 NPs can enter the human body through different ways and accumulate in the body, posing a threat to human health.**

Before the rise of nanotechnology, TiO2 was established in the form of fine atoms (FPs), that were thought-out as poor dissolved and reduced toxicity pieces.[6] However, few studies have belied this view, to a degree lung tumors in rats unprotected to extreme levels of TiO2 FPs for two age.[7] Furthermore, TiO2 has happened top-secret all at once 2B cancer-causing agent (possibly malignant to persons) for one International Agency for Research on Cancer.[8] Although the distinguishing carcinogenicity of TiO2 FPs is still discussed, skilled is certainly that TiO2 FPs pose a health risk.[9] Compared to TiO2 FPs, TiO2 NPs present more powerful catalytic action and bioactivity on account of their nano scale ranges.[9] Consequently, the toxicity of TiO2 NPs cannot be alone implicit from the known toxicology of TiO2 FPs, nor calm have in mind utilizing normal forms.[10] In current age, extensive investigation of the belongings of TiO2 NPs uncovering on human strength more indicates the high concern about the security of TiO2 NPs. In addition to seeing all appropriate uncovering sketches and organic in-between steps, understanding the final poisonous consequence is fault-finding for human well-being risk estimate.[11] Results from another teenager cohort study in China determined that Ti can cross the placental obstruction (PB) to harm fetuses that are intensely alert referring to practices or policies that do not negatively affect the environment warnings.[12] Several epidemiological studies have habitual that Ti exposure increases the risk of un favourable beginning consequences, containing affecting animate nerve organs hose defects, preterm beginning, fetal distress, and depressed beginning pressure.[13–15] Moreover, TiO2 NP uncovering can have disadvantageous belongings on the health of the society further the embryo. Emerging epidemiological evidence plans that greater levels of urinary or ancestry Ti are guide an increased risk of differing un favourable well-being belongings, containing diabetes and cardiopulmonary disorders (Figure 2).[16–19] In current years, lab studies on the toxicity of TiO2 NPs have surpassed epidemiological studies. Common animal models to a degree rodent, rats, zebra fish, and Drosophila have existed used to study TiO2 NPs. In vivo, studies have proved that TiO2 NPs uncovering can be linked to body part redness, pneumoconiosis or anthracosis, heart failure, generative toxicity, retinal

deteriorations, etc.[20–24] In vitro, studies have further supported these poisonous belongings of TiO2 NPs.[25–28] Given that nanoparticles can record the intelligence, concerns concerning their neurotoxic belongings, including those of TiO2 NPs, have acquire meaningful consideration.[29]

The entry of TiO_2 NPs into the brain mainly occurs through the blood-brain barrier (BBB), via absorption-mediated transversion or intranasal pathways.[30-31] However, the mechanisms by which nano-titanium dioxide penetrates and targets different brain regions remain unknown. The degree of TiO_2 NPs accumulation in each brain region closely correlates with the extent of neurotoxic effects. Common neurotoxic effects include behavior deficits, nervous system dysfunction, and structural changes induced by oxidative stress, autophagy, inflammation, or the activation of specific signaling pathways.[32] Although emerging studies support the role of TiO_2 NPs exposure as an environmental risk factor for human health, conscientious and systematic investigations are scarce into the extent of TiO_2 NPs translocation to different brain regions and the resulting damage to the neuronal system in relation to particle dose and particle size. The lack of information on the neurotoxicity of TiO_2 NPs also complicates risk assessment following exposure. Therefore, this paper will mainly focus on current studies concerning the neurotoxicology of TiO_2 NPs, while also reviewing the molecular mechanisms underlying their neurotoxic effects to mitigate potential damage resulting from exposure.[33]

2.Evidence from Epidemiological and Human Exposure Studies

In earlier years, population exposure to TiO_2 NPs was primarily investigated among occupational populations. Welding fumes, industrial waste combustion, and mineral mining can all result in environmental contamination by TiO_2 NPs, thereby increasing the exposure risk for workers.[33] Exposure to fumes from metal-inert gas soldering has been found to increase the risk of Parkinson's disease (PD).[34] Although these fumes mainly consist of zinc, copper, and iron, Andujar et al discovered an excessive accumulation of Ti in the lung tissue sections of welders in 2014.[35] Industrial waste, pesticides, and automobile exhaust are common sources of environmental pollutants associated with neurotoxic effects.[36] Among various environmental pollutants, NPs can easily penetrate the BBB and induce neurotoxicity by activating innate immune responses in astrocytes, microglia, and neurons.[36] TiO_2 NPs are a major component among environmental pollutants, with up to 760 tons of TiO_2 NPs being released into the soil through sewage and sludge each year.[37,38] Currently, there is no direct evidence of neurotoxic effects caused by TiO_2 NPs exposure in mineral miners, but a previous study suggested a significantly increased inflammatory response in mineral miners exposed to TiO_2 NPs.[39] It is well known that the occurrence of inflammatory reactions in other organs is closely related to nervous system damage.[40] With the increasing application of TiO_2 NPs, concerns have also arisen regarding the neurotoxic effects of non-occupational populations exposed to TiO_2 NPs. A recent cohort study demonstrated that high levels of urinary Ti during pregnancy were significantly associated with impaired language

development, suggesting that TiO_2 NPs might act as developmental neurotoxicants.[41] Furthermore, elevated levels of Ti in maternal hair were also significantly associated with an increased risk of neural tube defects.[42] However, epidemiological studies on the neurotoxic effects caused by TiO_2 NPs are still limited. Currently, laboratory studies are the main basis for evaluating the neurotoxicity of TiO_2 NPs.

3.Data Search

A review of the neurotoxic potential of TiO2 NPs was performed by a literature search of the PubMed database from 2021 to October 10, 2025 using combinations of the following keywords: Titanium dioxide nanoparticles exposure; E171 exposure; Titanium dioxide nanoparticles neuron; Titanium dioxide nanoparticles brain; Titanium dioxide nanoparticles behavior; and Titanium dioxide nanoparticles neurotoxicology. We used a two-step approach: initial screening of all titles and abstracts followed by full-text review of pertinent review articles, with one hundred forty-seven papers selected, including one hundred twenty-one research papers, and citations within twenty-six reviews screened for additional studies not identified in the electronic search, but no additional research papers were found through these references.

We identified studies that had administered TiO2 NPs to the organism in vitro or in vivo for experimental research; the organism groups studied primarily consisted of rodents, zebra fish, and cells, with fifty-five studies done on rodents, twenty on zebra fish, two on Caenorhabd itis elegans (C. elegans), one on each of Pheretima hawayana, Tegillarca granosa, and Drosophila melanogaster, and forty-one using in vitro cells, including animal and human-derived neuronal cells (Figure 3). [43]

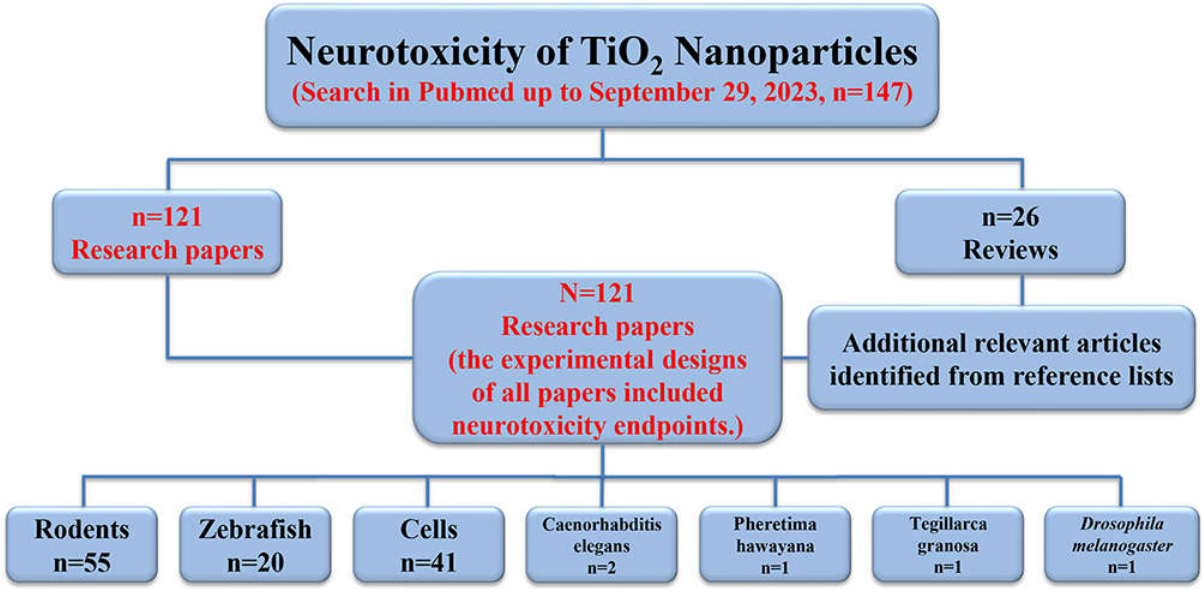


Figure 3 Study selection flow diagram. The flow chart illustrates the number of citations and resources that underwent screening, exclusion, and/or inclusion in the review.

4.Neurotoxic Effects of TiO2 NPs in Zebra fish

Zebrafish (Danio rerio) is commonly used as in vivo model system for studying the toxicity of nanomaterials due to its low cost, rapid growth, and significant homology to humans.[44] A total of 20 studies have investigated the neurotoxic effects of TiO2 NPs in zebrafish, with 11 of them examining co-exposure to other compounds (Table 3). Among the 11 studies, 8 studies selected the embryonic stage of zebrafish for TiO2 NPs exposure, 2 studies selected adult zebrafish, and one study selected zebrafish larvae. The most commonly used dose of TiO2 NPs in studies involving co-exposure to other compounds was 100 μg/L. So far, TiO2 NPs have been shown to enhance Pb,106,107 decabromodiphenyl oxide (BDE209),108 cypermethrin,109 triphenyl phosphate,110 bisphenol A,111,112 difenoconazole,113 tetracycline,114 and microcystinLR115 -induced neurotoxicity. TiO2 NPs mainly enhance the neurotoxicity of these compounds by increasing their bio concentration and bioavailability in zebrafish. Interestingly, co-exposure with TiO2 NPs did not alter pentachlorophenol-induced neurotoxicity.[45] Exposure to TiO2 NPs alone is also able to induce a variety of neurotoxic effects in zebrafish. The embryonic stage of zebrafish is the most commonly used exposure stage for TiO2 NPs exposure models, which may be attributed to the incomplete development of the BBB during this period.[46] TiO2 NPs exposure during the embryonic stage of zebrafish significantly alters motor behavior, social behavior, and spatial recognition memory.[47-50] In addition to behavioral impairments, TiO2 NPs exposure causes oxidative stress, promotes neuronal proliferation, decreases motor neuron axon length, alters gene expression, and increases cell apoptosis.[51-54] Two study chose the adult stage of zebrafish for TiO2 NPs exposure, and their results suggested that TiO2 NPs exposure caused cognitive deficit, promoted neuroinflammation, and altered biochemical constituents of the brain.[55-56]

Model System	Particle Size	Exposure Dose	Neurotoxic Effects	Ref.
Zebrafish embryos	5 nm	0, 100 μg/L	Enhanced Pb-induced neurotoxicity	[106]
	5 nm	0, 100 μg/L	Enhanced BPA-induced neurotoxicity	[111]
	5–10 nm	0, 100 μg/L	Enhanced DIF-induced neurotoxicity	[113]
	7.04 nm	0, 100 μg/L	Enhanced Pb-induced neurotoxicity	[107]
	7.04 nm	0, 100 μg/L	Enhanced BDE-209-induced neurotoxicity	[108]
	7.04 nm	0, 1 mg/L	Enhanced CYP-induced neurotoxicity	[109]
	100, 300 nm	0, 100 μg/L	Enhanced TPhP-induced neurotoxicity	[110]
	25 nm	0, 100 μg/L	No changed PCP-induced neurotoxicity	[116]
	6.5 nm	0, 5, 10, 20, 40 μg/L	Decreased spatial recognition memory, Altered biochemical constituents of the brain, Over proliferation of glial cells, Cell apoptosis	[117]
	7.04 nm	0, 0.1 mg/L	Altered motor and social behaviors, Cell apoptosis, Oxidative stress, Promoted neuronal proliferation	[118]
	14.1 ± 0.6 nm	0, 0.1, 1 mg/L	Altered motor and social behaviors, Cell apoptosis, Oxidative stress	[119]
	21 nm	0, 0.01, 0.1, 1.0 mg/L	Altered motor behavior, Decreased CNS neurogenesis, Decreased motor neuron axon length, Altered gene expression	[120]
	30 nm	0, 100 μg/L	Cell apoptosis	[121]
	33.4 ± 1.9 nm	0, 0.1, 1, 10 μg/mL	Oxidative stress, Loss of DA secretion, Altered gene expression	[122]
	50 nm	0.1 mg/mL	Oxidative stress	[123]
Zebrafish larvae	/	0.5 mg/L	Enhanced TC-induced neurotoxicity	[114]
Adult zebrafish	5 nm	0, 100 μg/L	Enhanced BPA-induced neurotoxicity	[112]
	26.98 ± 0.85 nm	0, 100 μg/L	Enhanced MCLR-induced neurotoxicity	[115]
	20 nm	0, 10, 100 ppm	Altered biochemical constituents of the brain	[124]
	/	10 μg/mL	Caused cognitive deficit, Caused neuroinflammatory	[125]

Note: The reported particle size reflects the diameter of primary particles.

Table 1. Overview of Literature Investigating Neurotoxic Effects of TiO2 NPs in Zebra fish

Result

Neurotoxic Effects of TiO2 NPs in vitro Models

In vitro models are widely used to assess neurotoxic effects on cellular functions.[57]Several studies have evaluated the neurotoxic effects of TiO2 NPs using in vitro models. Primary hippocampal and cortical neurons are widely used in vitro models for neurotoxicology testing as they are easily polarized and form unique axons and dendrites. In addition, these models are used to study neuronal polarization, axon/dendrite morphology, synaptic formation, and central nervous system (CNS) functions.[58] Exposure to TiO2 NPs impairs neuronal function, inhibits neuroblast proliferation, reduces cell viability, and increases cell apoptosis by promoting oxidative stress in both primary hippocampal and cortical neurons.[59–64] Furthermore, TiO2 NPs inhibit neurite outgrowth of hippocampal neurons by interfering with glutamate metabolism and impairing N-methyl-D-aspartic acid (NMDA) receptor function.[65] According to some previous studies, the suppression of axonal development, dendritic development, and synapse development by TiO2 NPs was associated with decreased expression of axon growth-related factors and inhibition of the Wnt/β-catenin and BDNF-TrkB pathways.[66-68] See Table 5 for details.

Rat pheochromocytoma (PC12) cell line and human SH-SY5Y neuroblastoma cell line have been used as models for neurotoxicity testing of TiO2 NPs (Table 5). PC12 cell line shows morphological and functional differentiation similar to sympathetic neurons. PC12 cell line is a suitable model for studying the chemical disruption of neuronal differentiation, synthesis, storage, and release of neurotransmitters, function and regulation of ion channels, and the interaction of compounds with membrane-bound receptors.[69] A previous study revealed that treatment of PC12 cells with TiO2 NPs (< 36 nm, < 200 μg/mL) decreased cell viability, increased cell apoptosis via oxidative stress, inhibited the neurite outgrowth, disturbed cell cycle, and disrupted the ubiquitin-proteasome system.[70–72] The human-derived SH-SY5Y cell line is preferred over the PC12 cell line as it avoids interspecific differences in chemical action.161 The SH-SY5Y cell line is an excellent model for studying toxicity on proliferating or differentiated cells because it can be maintained as neuroblasts or induced to differentiate into more neuron-like morphologies.[73] TiO2 NPs were shown to cause endoplasmic reticulum (ER) stress, autophagy, inhibition of cell proliferation, disturbance of the microtubule dynamics, and membrane damage in SH-SY5Y cells.[74–79] Several in vivo studies investigated the neurotoxic effects of TiO2 NPs on mouse hippocampus. However, one in vitro study explored the neurotoxic effects of TiO2 NPs on mouse hippocampal neuronal HT22 cells. The study revealed that TiO2 NPs increased apoptosis of HT22 cells via oxidative stress- and calcium imbalance-mediated ER stress.[80]

Acute or prolonged exposure to TiO2 NPs is associated with toxic effects on neuronal and glial cells.[81] Glial cells are critical cells of the nervous system, which serve as tissue-resident macrophages. Microglia are crucial regulators that influence nervous system development, maintenance of the neural environment, and response to injury and repair.[82] The immortalized mouse microglia cell line BV2 is often used as an alternative for primary microglia in cell experiments. Some previous studies showed that exposure of BV2 cells to TiO2 NPs was associated with mitochondrial dysfunction and increased oxidative stress.[83-84] Astrocytes play a key role in innate and adaptive immune responses in CNS injury.[85] Due to advancements in cell culture technology, primary astrocytes have become a common primary cell model. Previous studies revealed that TiO2 NPs induced mitochondria damage, oxidative stress, autophagy, neuro inflammation, and cell apoptosis in primary rat cortical astrocytes.[86–88]

Other studies employed human glial cell lines as in vitro models for neurotoxicity studies to eliminate species differences. Some previous studies revealed that TiO2 NPs

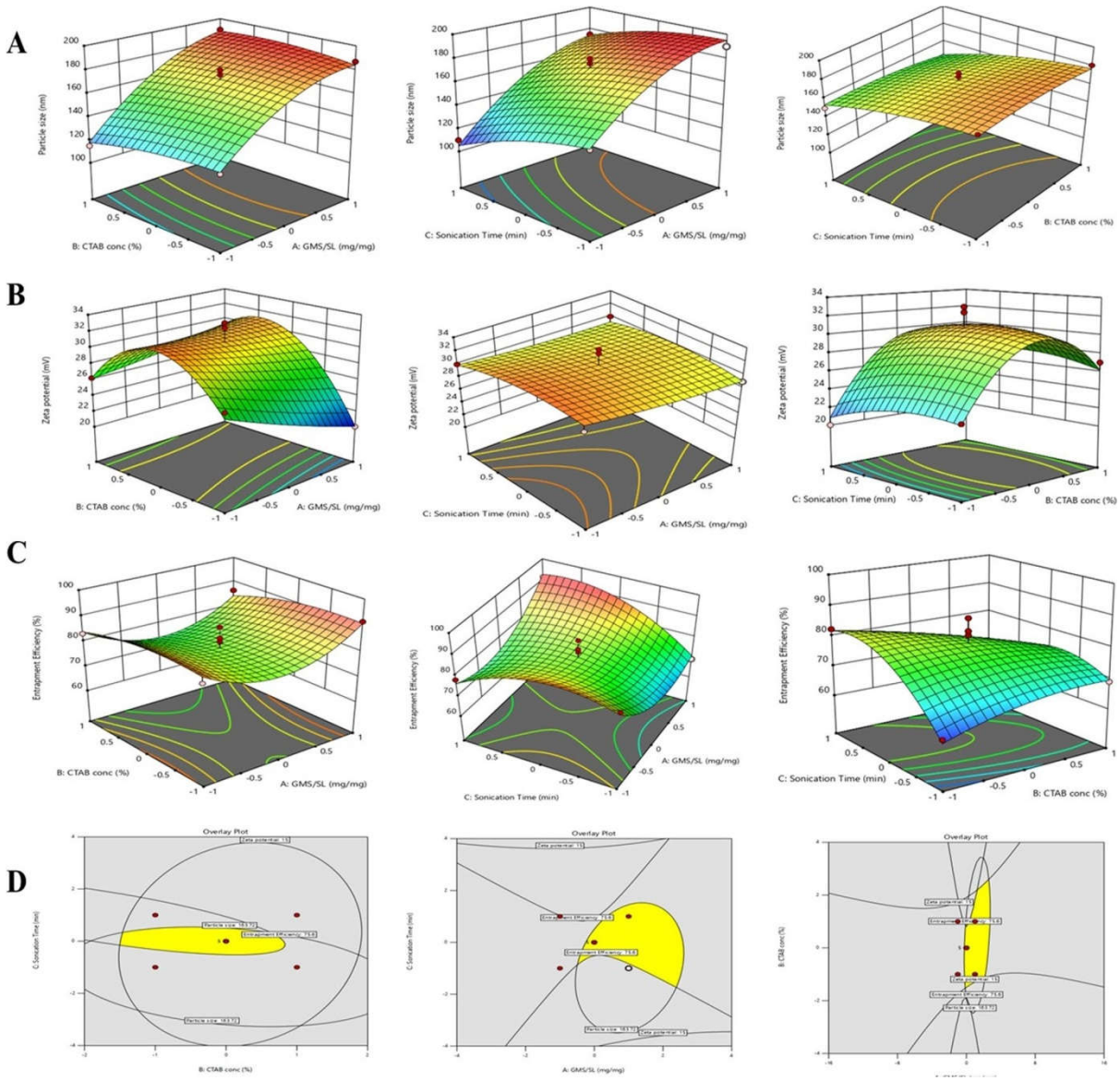


Fig.1A Responsesurfaceplotforeffectofallindependentvariablesonvesiclesize.**B**Zetapotential.**C**Entrapmentefficiency.**D**Overlaypl

Model System	Particle Size	Exposure Dose	Neurotoxic Effects	Ref.
Primary hippocampal rat neurons	5.5 nm	0, 5, 15, 30 μg/mL	Decreased cell viability, Increased levels of LDH, Cell apoptosis	[139]
	5.5 nm	0, 5, 15, 30 μg/mL	Inhibited neurite outgrowth by interfering with glutamate metabolism, Impaired NMDA receptor function	[145]
	5.5 nm	0, 1.25, 2.5, 5 μg/mL	Inhibited dendritic development, Inhibition of the Wnt/β-catenin pathway	[147]
	36.83 nm	0, 5, 15, 30 μg/mL	Inhibited axonal development	[146]
	/	0, 5, 15, 30 g/mL	Inhibited synapse development, Inhibition of the BDNF-TrkB pathway	[148]
Primary rat cortical neurons	26.2 ± 10.7 nm	0, 30, 100 μg/mL	Limited hazard for neuronal function	[140]
	6–142 nm	0, 3.1, 6.3, 12.5, 50 μg/mL	Decreased cell viability	[141]
	200–700 nm	0, 5, 10, 15, 20 μg/mL	Decreased proliferation of neuroblasts	[142]
Primary mouse cortical neurons	20–80 nm	20, 50 mg/cm^2	Oxidative stress	[144]
	< 100 nm	0.01–300 μg/cm^2	Oxidative stress	[143]
PC12 cells	20–50 nm	0, 10, 50, 100 μg/mL	Oxidative stress Cell apoptosis	[149]
	< 25 nm	0, 50, 100, 200 μg/mL	Oxidative stress, Dysfunction of the ubiquitin-proteasome system, α-Syn aggregation	[150]
	< 36 nm	0, 0.01, 0.1, 1, 10, 100 μg/mL	Inhibited the neurite outgrowth	[151]
	Anatase-20 nm Rutile-20 nm Micro-1000 nm	0, 25, 50, 100, 200 μg/mL	Decreased cell viability, Increased levels of LDH, Oxidative stress, Cell apoptosis, Disturbed cell cycle, Altered gene expression	[152]
SH-SY5Y cells	5 nm	0, 5, 10, 50, 100 μg/mL	Cell apoptosis, Oxidative stress, ER stress	[153]
	20 nm	0, 2, 10, 50, 100 μg/mL	Disturbed cell cycle, Oxidative stress, Membrane damage, Autophagy	[154]
	25 nm	0, 80, 120, 150 μg/mL	Disturbed cell cycle	[155]
	100–150 nm	0, 100 μg/mL	Altered cellular morphology, Disturbed the microtubule dynamics	[156]
	115.73 ± 0.67 nm	0.75–75 μg/mL	Inhibited cell proliferation	[157]
	/	0, 5, 10, 20, 40, 80, 160 μg/mL	Decreased cell viability, Increased levels of LDH, Promoted inflammation	[158]
HT22 cells	50 nm	0, 50, 100, 200 μg/mL	Cell apoptosis, Oxidative stress, ER stress	[159]

Note: The reported particle size reflects the diameter of primary particles.

Table 5 Overview of the Literature on Neurotoxic Effects of TiO2 NPs on Primary Neuron and Nerve Cell Lines

inhibited cell proliferation, induced morphological changes, decreased immuno-location of F-actin fibers, and increased cell apoptosis in U374 cells.[89-90] Furthermore, several studies have investigated the neurotoxic effects of TiO2 NPs in a co-culture of glial cells and other cells. For example, Yang et al showed that TiO2 NPs stimulate the inflammatory reaction in brain microglia and damage neuron using a co-culture model of primary microglia and PC12 cell line.[91] Similarly, TiO2 NPs was shown to stimulate the inflammatory reaction in brain microglia and damage neurons in co- culture models of BV2 and N27 mesencephalic neurons, and BV2 and N2a neuroblastoma cells.[92-93] See Table 6 for details.

Most in vivo and in vitro studies have evaluated the neurotoxic effects of TiO2 NPs in the cortex, hippocampus, and cerebellum. However, to the best of our knowledge, no studies have evaluated the neurotoxic effects of TiO2 NPs on other brain regions. The BBB is effective in protecting the brain from chemical damage. Therefore, there is a need to understand the effects of TiO2 NPS on the BBB. A previous study exploring the effects of TiO2 NPs on an in vitro model of BBB established by co-culturing primary human brain micro vascular endothelial cells (HBMECs) and primary human astrocytes, revealed that TiO2 NPs increased the permeability of the BBB.[94] Another study showed that acute or long-term exposure of an in vitro model of the BBB established by co-culturing primary rat endothelial cells and glial cells to TiO2 NPs was associated with BBB dysfunction related to increased inflammatory response and altered expression of the ABC transporter.[95] Moreover, treatment of T98G human glioblastoma cells with TiO2 NPs was associated with changes in the transcriptome, suggesting that exposure to TiO2 NPs could compromise BBB integrity and cause neuroinflammation.[96] Furthermore, TiO2 NPs can be internalized by dorsal root ganglion cells (DRG) and cause damage via apoptosis.[97-98] Yu et al showed an association between the toxic effects of TiO2 NPs on olfactory bulb neuron cells and its pathogenicity to

neurodegenerative diseases.[99] Furthermore, exposure to TiO2 NPs was associated with varying degrees of cytotoxicity to the human cerebral endothelial cell line (HCECs), human neural stem cell line (hNSCs), and neuroectodermal stem cell line (1C11) models.[100–102] See Table 7 for details.

Table 6 Overview of the Literature on Neurotoxic Effects of TiO2 NPs in Primary Glial Cells and Glial Cell Lines

Model System	Particle Size	Exposure Dose	Neurotoxic Effects	Ref.
BV2 microglia	20–30 nm	0.1–200 μg/mL	Mitochondrial dysfunction, Oxidative stress	[28]
	30 nm	2.5–120 ppm	Oxidative stress, Mitochondrial dysfunction	[164]
Primary rat cortical astrocytes	10, 20 nm	0, 6.25, 12.5, 25, 50, 100 mg/L	Cell apoptosis, Morphological changes	[168]
	50 nm	116 μg/mL	Mitochondria damage, Oxidative stress, Autophagy, Neuroinflammation	[167]
	Anatase-360 nm P25-540 nm Rutile-360 nm	0, 25, 50, 100 mg/kg	Mitochondria damage, Oxidative stress	[166]
C6 and U373 cells	< 50 nm	0, 20 $\mu g/cm^2$	Oxidative stress, Mitochondrial damage, Cerebral damage, Neurodegenerative diseases	[170]
	40–200 nm	0, 2.5, 5, 10, 20, 40 $\mu g/cm^2$	Inhibited cell proliferation, Morphological changes, Decreased immuno-location of F-actin fibers, Cell apoptosis	[169]
Primary microglia and PC12 cells	20 nm	0, 0.25, 0.5 mg/mL	Neuroinflammation	[171]
BV2 microglia and N27 mesencephalic neurons	< 330 nm	2.5–120 ppm	Promoted inflammation, Cell apoptosis, Altered cell cycle, Decreased energy metabolism	[172]
Human astrocytoma cells-D384 and SH-SY5Y cells	69.3 ± 0.4 nm	0, 15, 31, 125 μg/mL	Disturbed cell cycle, Membrane damage, Mitochondrial dysfunction	[162]
BV2-N2a, ALT-N2a, ALT-BV2 co-culture	44.4 ± 0.2 nm	0, 5, 30, 100 μg/mL	Decreased cell viability, Oxidative stress, Promoted inflammation	[173]

Note: The reported particle size reflects the diameter of primary particles.

Factors Influencing the Neurotoxic Potential of TiO2 NPs

The neurotoxic effects of TiO2 NPs are influenced by various factors. The exposure characteristics, such as exposure dose, method, duration, and species, can influence the toxic effects of TiO2 NPs in vivo. A review of the literature showed that the exposure dose in vivo and in vitro experiments was larger than the actual exposure dose of the population. According to a previous study, the levels of TiO2 NPs in air and water ranged from 0.7 to 16 μg/L.182 It is estimated that children have an intake of TiO2 NPs of about 2–3 mg/kg/day, while adults have a TiO2 NPs intake of about 1 mg/kg/day.2 Human exposure to TiO2 NPs is mainly through dietary intake and air inhalation. Although the exposure methods selected in animal studies attempted to mimic human exposure closely, there are some gaps. For example, the system for intranasal administration is simple compared to inhalation administration. Furthermore, intranasal administration is significantly affected by the inhalational dose.[103] The intranasal administration volumes in rodents at a given time should be limited to approximately 5 μL per nostril since volumes greater than this are likely to become wasted.[104,105] Furthermore, ingested TiO2 NPs first interacts with the oral mucosa. However, intragastric administration does not interact with the oral mucosa and is thus associated with significant differences in absorption, bioavailability, and metabolism with implications for assumptions and models of toxicity kinetics.[106] In addition, the exposure period and duration also influence the neurotoxic effects of TiO2 NPs.[107-108] However, the exposure duration in experiments tends to be shorter than that in humans. Species differences

are often unavoidable. Therefore, there is a need to conduct epidemiological studies exploring the neurotoxic effects of TiO2 NPs on humans.

Furthermore, the physical and chemical properties of TiO2 NPs can affect their neurotoxicity. Particle size is key. In general, small particles are more likely to be absorbed and thus exert toxic effects.[109] According to some previous studies, the neurotoxic effects of TiO2 NPs depend on particle size.110,120 The hydrodynamic diameter or secondary particle sizes of TiO2 NPs are important with respect to neurotoxicity. While smaller NPs may seem more neurotoxic, they are also more likely to clump together and form aggregates.121 Theoretically, the particle aggregation would increase the effective particle size thus reducing the neurotoxic potential. Several studies have used dynamic light scattering (DLS) to determine the effects of hydrodynamics or secondary particle size of TiO2 NPs on neurotoxicity. However, no studies have explored the effect of aggregate particle size on the neurotoxicity of TiO2 NPs. The zeta potential of TiO2 NPs has also been investigated in most neurotoxicological studies. Since most cell membranes are negatively charged, the zeta potential affects the tendency of NPs to penetrate the membrane, with cationic particles generally exhibiting higher toxicity associated with cell wall damage.187 Furthermore, the surface charge of the nanoparticles can determine the degree of aggregation.122,123,124 However, further studies are needed to investigate whether the zeta potential affects the neurotoxicity of TiO2 NPs. In addition, the toxicity of TiO2 NPs is dependent on crystalline phases. The anatase form of TiO2 NPs is more neurotoxic than that of rutile TiO2 NPs and P25 TiO2 NPs since anatase has a higher ability to induce oxidative stress.125,126, 127 Taken together, various factors can affect the neurotoxic potential of TiO2 NPs, including physical and chemical properties of TiO2 NPs, and exposure dose, exposure duration, exposed species. However, the specific effects of these factors on the neurotoxic effects of TiO2 NPs still need to be systematically compared.

Reflections on Neurotoxicity Induced by TiO2 NPs

Most studies to date have focused on rodents, and most experimental exposures used are not very realistic for human exposure. In addition, there is currently limited information on the levels of TiO2 NPs in the environment, consumer goods, and food products. For humans, more accurate monitoring is needed to determine daily exposure levels, particle characteristics and exposure route, all of which affect the neurotoxic potential of TiO2 NPs. Evaluating and availing data on TiO2 NPs levels in different environmental media helps to reliably estimate human exposure and thus assess the risk of TiO2 NPs. Furthermore, the degree of uptake through the digestive system, respiratory system, potential BBB crossing, and potential translocation to or even accumulation in nervous system should be further investigated. This information will indicate which route of exposure mitigation is most valuable for human health protection. However, apart from the recommended exposure limits (REL) established by the National Institute for Occupational Safety and Health (NIOSH), no other regulatory agencies have set occupational or environmental exposure limits for TiO2 NPs.9 There are limitations in the monitoring methods of TiO2 NPs. There is an urgent need to develop appropriate methods for reducing TiO2 NPs in environmental media and food to prevent their potentially harmful health effects.128

The specific mechanisms behind the neurotoxic effects of TiO2 NPs have only been explored through animal and cell experiments. TiO2 NPs increase the formation of reactive oxygen species (ROS) in the brain, thus inducing oxidative stress. Ze et al reported that TiO2 NPs induced oxidative stress thus causing brain damage through over activation of the p38-Nrf-2 signaling pathway.78 Oxidative stress can induce neuro inflammation, thus further aggravating cell damage.129,130,131 Cell damage, including structural and functional damage, is associated with increased onset and development of neuro developmental or neurodegenerative diseases, such as autism spectrum disorder (ASD) and PD.87,100 Cell damage is also linked to behavioral deficits.132,143 Abnormal motor ability could be caused by a decrease in the axon length of motor neurons.144 In addition, changes in hippocampal synaptic plasticity could lead to decreased spatial recognition.145 The development of axons, dendrites and synapses is regulated by various signaling pathways. TiO2 NPs impair the growth of axons and dendrites through excessive activation of the ERK1/2/MAPK signaling pathway.146 In addition, impairment of dendritic growth by TiO2 NPs is also related to inhibition of the Wnt/β-catenin signaling pathway.147 Moreover, suppression of the neuronal synaptic outgrowth by TiO2 NPs is linked to the inhibition of the BDNF-TrkB signaling pathway.147-148 Furthermore, the accumulation of TiO2 NPs in the brain could cause alterations in brain biochemistry and changes in neurotransmitter levels, contributing to behavioral changes.149-160,161-168 Although all of these studies confirm that TiO2 NPs cause neurotoxic effects through different mechanisms, most of the evidence on the neurotoxic effects of TiO2 NPs is fragmentary and is obtained from different species. Furthermore, few of these mechanism studies have explored whether the neurotoxic effects of TiO2 NPs are mediated through synergistic interactions of multiple brain regions, organs, and systems. Whether TiO2 NPs with different characteristics cause different degrees of toxic effects through different mechanisms remains be further explored. Extensive systematic studies are needed to fully elucidate the neurotoxic mechanisms of TiO2 NPs, which will be helpful for the prevention and treatment of neurotoxic effects of TiO2 NPs.

Conclusion

Animals and humans can be exposed to TiO2 NPs through different exposure pathways, thus posing health hazards. At present, the neurotoxic effects of TiO2 NPs have only been evaluated through animal models, including rats, mice, and zebra fish, and cell studies, including primary neurons, PC12, and SH-SY5Y cell lines. TiO2 NPs can induce oxidative stress, promote neuro inflammation, alter brain biochemistry, or damage neurons. Neuronal damage can further lead to various behavioral disorders and is closely associated with increased onset and development of neuro developmental or neurodegenerative diseases. However, due to the lack of relevant epidemiological studies, whether TiO2 NPs are linked to neuro developmental or neurodegenerative diseases in humans remains unknown. Furthermore, the neurotoxic potential of TiO2 NPs can be affected by various factors. There is a need for researchers to understand the neurotoxic effects of TiO2 NPs on humans and develop strategies for mitigating the effects of TiO2 NPs on human health.

Abbreviations

NMs, nanomaterials; TiO_2 NPs, titanium dioxide nanoparticles; FPs, fine particles; PB, placental barrier; BBB, blood- brain barrier; *C. elegans, Caenorhabditis elegans*; SD rats, Sprague-Dawley rats; PND, postnatal day; BDNF, brain- derived neurotrophic factor; BW, body weight; BDE-209, decabromodiphenyl oxide; NMJ, neuromuscular junction; AchE, acetylcholinesterase; MDA, malondialdehyde; CNS, central nervous system; NMDA, N-methyl-D-aspartic acid; ER, endoplasmic reticulum; HBMECs, human brain microvascular endothelial cells; DRG, dorsal root ganglion; HCECs, human cerebral endothelial cell line; HNSCs, human neural stem cell line; 1C11, neuroectodermal stem cell line; DLS, Dynamic light scattering; REL, recommended exposure limit; NIOSH, National Institute for Occupational Safety and Health; ROS, reactive oxygen species; ASD, autism spectrum disorder; PD, Parkinson's disease

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