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Toxicological aspects of titanium dioxide nanoparticles in relation to different organs

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Abstract

Nano-sized titanium dioxide particles belong to most widely manufactured Nanoparticles (NPs) on a global scale because of their unique properties. TiO_2 NPs are among the top five nanoparticles used in consumer products. In the present chapter, an attempt has been made to compile the available reports revealing the toxic effects of these nano-moieties. TiO_2 NPs may be either ingested or inhaled into the human body through most common routes of exposure including oral-gastrointestinal tract and lungs. Inhaled TiO_2 NPs have been demonstrated to cause negative health impacts including respiratory tract cancers in rats. Various human oral and lung cell lines have been utilized in different studies to evaluate the cytotoxicity after treatment with distinctive sizes and shapes of TiO_2 NPs. Their overload has been found to induce genotoxicity, lung inflammation and even lung cancer. These nanoparticles have also been reported to stimulate oxidative stress and carcinogenic effect on human liver. Exposure to TiO_2 NPs reduces the number of neurons, induce apoptosis and instigate inflammation in rat brain. Conclusively, human exposure to TiO_2 NPs should be minimized so as to reduce the associated risk.

Introduction

Titanium (Ti) with atomic number 22 is a hard silvery grey metal of the transition series. Titanium is widely distributed and occurs about 0.44% in earth crust. Its two prime commercial minerals are limenite and rutile. It resembles other transition metals such as nickel and iron in being hard and refractory with high corrosion and resistance. Titanium is used for making watches, bracelets and even heavy machineries including aircrafts, missiles and spacecrafts. Ti is also used as a deoxidizer in steel to reduce grain size and in copper to produce hardening. It is used as a surgical aid to repair fractures. Titanium exhibits +2, +3, +4 oxidation states and its oxides exist as titanium monoxide, titanium dioxide, di-titanium dioxide and titanium trioxide. Titanium Dioxide (TiO_2) is also called titania and it naturally occurs in crystalline form. Oxide forms of Ti are mined and serve as a useful source for commercial titanium. TiO_2 is called titanium white or pigment white 6, when used as a pigment. The photocatalytic activity of TiO_2 results in thin coating exhibiting self-cleaning and disinfecting effect under exposure to UV radiation. TiO_2 is used as thickening, whitening and lubricating agent and as sunscreen ingredient in cosmetics. It protects skin from UV-A and UV-B radiations. TiO_2 is used in food products like candies and chewing gums and food packaging. As it exhibits high corrosion resistance, it can withstand high temperatures. TiO_2 is used in other products such as paints, papers and inks. TiO_2 is used in laundry and dishwashing products, electronic products, lubricating additive, catalyst and making rubber tyres.

Nanoparticles are the particles having sizes between 1 and 100 Nanometres (nm) with a surrounding interfacial layer. Production, as well as use of TiO_2 NPs is rapidly increasing. Nanoparticles exist in the natural world and are also created as a result of human activities. Nanoparticles are of great scientific interest as they act as a bridge between bulk materials and atomic or molecular structures. Nano-sized TiO_2 particles belong to most

widely manufactured nanoparticles on a global scale because of their photocatalytic activity and related surface effect. TiO_2 NPs are in the top five nanoparticles used in consumer products [1]. The nano-sized particles are attracting scientific community due to their wide range of applications. Nanomaterials are at the leading edge of the rapidly developing field of nanotechnology [2]. Increased use of nanomaterials in industry and biomedicine poses potential risks to human health and the environment. The intensive use of TiO_2 NPs in sunscreens, toothpastes and medications make humans exposed to it daily, which increases health risks. The toxicity of TiO_2 NPs is a controversial subject. TiO_2 NPs may exhibit ill effects on animal health and after TiO_2 NPs inhalation, studies have demonstrated lung cancer in rats [3]. The over-doses of TiO_2 NPs induced genotoxicity in lungs associated with inflammation, which also amplified oxidative stress. Fe_2O_4-TiO_2 NPs and TiO_2 NPs have also been reported to show toxic effects on human liver cell line HL7702 cells [4]. The present paper reviews the available reports to assess the toxicological aspects of TiO_2 NPs in relation to lungs, liver and brain.

Pneumotoxicity

The word pneumotoxicity refers to having a toxic effect on lungs. Pneumotoxicity is not only restricted to a hypersensitivity reaction or bronchospasm. It can affect all anatomical structures of the lung. Although most cases of pulmonary toxicity in medicine are due to side effects of medicinal drugs. Many cases out of these can be due to side effects of radiotherapy. Other causes of pulmonary toxicity may include chemical compounds and airborne particulate matter including nanoparticles. Pneumotoxicity can include lung inflammation or pneumonitis, secondary lung infection, organising pneumonia (bronchiolitis obliterans organising pneumonia, BOOP), lung fibrosis, Acute Respiratory Distress Syndrome (ARDS), solitary pulmonary mass including lung cancer or formation of pulmonary nodules.

Studies related to pneumotoxicity on rats

Inhaled TiO_2 NPs can have undesirable health effects which have been reported to cause respiratory tract cancer in rats. In a study, a wide range of complementary endpoints have been taken to study TiO_2 P25 NP-induced genotoxicity, in lung overload as well as non-overload conditions. Additionally, inflammation, lung burden, cytotoxicity and oxidative stress have also been evaluated in order to find a relation between genotoxicity and these responses. The study confirmed that for total particle surface area lung deposition or 4.2 µl/kg for volume-based cumulative lung exposure dose, the lung overload threshold finds a place at approximately 200-300 cm^2 of lung burden. Above this value, inflammation is induced and lung clearance is impaired. The results also revealed that these overload doses induced delayed genotoxicity in lung which were associated with persistent inflammation only at the highest dose. The lowest tested doses were found to have no toxicity or genotoxicity effects in the lungs [3]. The exposure of Ferric Oxide (Fe_2O_3) and TiO_2 NPs induced oxidative stress on mouse lung and bone marrow cells was investigated. The oxidative stress induced by NPs was determined by measuring its indicators such as antioxidant scavenging activity of superoxide dismutase and catalase as well as malondialdehyde concentration. In addition, the maximum level of oxidative stress derived from TiO_2 NPs was observed in both tissue types. Co-treatment with NPs and the antioxidant α-tocopherol reduced antioxidant activities and membrane Lipid Peroxidation (LPO) in the lung cells suggesting that oxidative stress may be the reason for the cytotoxic effects of NPs [4].

The number of workers potentially exposed to NPs during industrial processes has increased. The short- and long-term pneumo-toxicological properties of TiO_2 were investigated. Fischer 344 rats were exposed to 10 mg/m^3 of a TiO_2 Nanostructured Aerosol (NSA) by nose-only inhalation for 6 h/day, 5 days/week for 4 weeks. Lung samples were collected for 180 post-exposure days in the experiment. Cytological and biochemical analyses of Bronchoalveolar Lavage (BAL) revealed a robust inflammatory response up to 3 post-exposure days. Genes involved in oxidative stress and vascular changes were up regulated. A persistent altered expression of various genes up to 180 exposure days was also seen as a long-term response [5].

Studies related to pneumotoxicity using human cell lines

TiO_2 NPs have become inevitable part of our daily life in the form of bio-medical, cosmeceutical and nano-pharmaceutical products. The TiO_2 NPs may be inhaled into the human respiratory system through common route of trachea and lungs. The increased applications of NPs in a wide range of industrial fields raise the concern about their potential toxicity to humans. A study assessed and compared the toxicity of four different oxide nanoparticles (Al_2O_3, CeO_2, TiO_2 and ZnO) to A549 carcinoma cells, human lung epithelial cells and L-132 normal cells. ZnO exhibited the maximum cytotoxicity in terms of cell viability, cell proliferation, membrane integrity as well as colony formation in both cell lines. Al_2O_3, CeO_2 and TiO_2 showed slight adverse effects on cell viability and cell proliferation, though oxidative stress was induced by TiO_2 in a time and concentration-dependent manner. CeO_2 instigated membrane damage and repressed colony formation, but with varied degrees depending upon cell lines. Al_2O_3 seemed to be less toxic in comparison to other nanoparticles even after long term exposures [6]. Another study showed that TiO_2 may induce apoptosis in H1299 lung cancer cells. TiO_2 NPs resulted in both a dose- and time-dependent reduction in cell viability. These NPs also appeared to involve necrosis as well as apoptosis. Expression of Id1 was significantly reduced in TiO_2-treated cells as compared to control cells [7]. Human colon and lung cells were exposed to test particles, TiO_2 NPs 18 nm, TiO_2 NPs 30 nm, and TiO_2 NPs 87 nm with a dose range 0.1-100 µg/ml. The TiO_2 NPs 18, TiO_2 NPs 30, and TiO_2 NPs 87 significantly ($p < 0.001$) reduced cell viability in a dose- and a size-dependent manner at 60 and 100 µg/ml. ROS levels increased significantly at doses 60 ($p < 0.01$) and 100 ($p < 0.001$) µg/ml in both types of cells. The smaller size particle, TiO_2 NPs 18 had produced a significant ($p < 0.05$) toxic effect even at the lowest dose i.e., 10 µg/ml. The result showed that TiO_2 NPs 18, TiO_2 NPs 30, and TiO_2 NPs 87 induced a dose- and size-dependent cytotoxicity via decreased cell viability, increased LDH and ROS levels [8].

Various human lung and oral cell lines were chosen to assess the cytotoxicity of treatment with different shapes and sizes of TiO_2 NPs. On the basis of endocytic behavior results and cell viability, treatment with all the selected TiO_2 NPs was found to be nearly non-toxic to the oral cell lines. However, high cytotoxicity was seen in lung cells with AFDC and M212 treatments at 50 µg/mL. Results also reported apoptosis resulting from the considerable aggregation of TiO_2 NPs in the cytoplasm. cNRs and AFDC could slow down the growth of lung cells and may permit a substantial proportion of the cells to stay in the G1/G0 phase [9].

Table 1: Studies presenting the toxic effects of titanium dioxide nanoparticles on lungs

S.No.	Author	Year	Model	Organ	Results	Reference No.
1	Relier *et al.*	2017	Rat	Lungs	Overload of TiO_2 NPs doses induced genotoxicity and inflammation in lung and caused lung cancer	3
2	Soltani *et al.*	2018	Rat	Lungs	Co-treatment with TiO_2 NPs and the antioxidant α-tocopherol reduced antioxidant activities and membrane Lipid Peroxidation (LPO) in the lung cells, but increased CSF-induced colony formation and oxidative stress	4
3	Chezeau *et al.*	2018	Rat	Lungs	Genes involved in oxidative stress and vascular change are up regulated due to long term exposure of TiO_2 NPs	5
4	Kim *et al.*	2010	Human	Lungs	Al_2O_3, CeO_2 and TiO_2 NPs showed little adverse effects on cell proliferation and cell viability. but, TiO_2 induced oxidative stress that was dose dependent	6
5	Lee *et al.*	2009	Human	Lungs	Exposure to TiO_2 NPs reduce cell viability and appeared to involve both necrosis and apoptosis	7
6	Gandamalla *et al.*	2018	Human	lungs	TiO_2 NPs 18, TiO_2 NPs 30, and TiO_2 NPs 87 induced cytotoxicity and decreased cell viability; increased LDH and ROS levels	8
7	Chen *et al.*	2015	Human	Lungs	Different sizes and shapes of TiO_2 NPs including AFDC and cNRs could inhibit the growth of lung cells and allow cells to remain in the G1/G0 phase; high-dose induced apoptosis in lungs	9

TiO_2 NPs: Titanium Dioxide Nanoparticles; LPO: Lipid Peroxidation; CSF: Colony Stimulating Factors; LDH; Lactic Acid Dehydrogenase; ROS: Reactive Oxygen Species

Hepatotoxicity

Hepatotoxicity implies chemical-driven liver damage. Drug-induced liver injury may be a reason of different acute and chronic liver diseases. The liver plays a key role in transforming various chemicals and is vulnerable to the toxic effects of these chemical agents. Some medicinal agents, if taken in overdoses may injure the organ. Sometimes even when introduced within therapeutic ranges, certain chemicals may prove to be toxic. Hepatotoxicity may include stomach pain, nausea, unusual tiredness, dark-coloured urine and jaundice.

Studies related to hepatotoxicity using human cell lines

To evaluate the toxicity and underlying molecular mechanisms of Janus Fe_3O_4-TiO_2 NPs, human liver cell line HL-7702 cells were used. For comparison, TiO_2 NPs were also evaluated. Results showed that both Fe_3O_4 -TiO_2 NPs and TiO_2 NPs decreased cell viability and ATP levels but increased Malondialdehyde (MDA) and Reactive Oxygen Species (ROS) generation. Cell viability analysis showed that TiO_2 NPs induced slightly higher cytotoxicity than Fe_3O_4 -TiO_2 NPs in HL7702 cells. Western blotting indicated that both TiO_2 NPs and Fe_3O_4 -TiO_2 NPs could induce apoptosis, inflammation and carcinogenesis [10]. The toxicity of TiO_2 NPs on human liver can be studied via a two-step approach, including a cell-response model and a Physiologically-Based Pharmacokinetic (PBPK) model. PBPK model forecasts the bio-distribution of NPs that remain in the human body after exposure and also shows accumulation of NPs in the liver tissue. Whereas, liver cell death as a consequence of the accumulated TiO_2 NPs is predicted by the cell-response model. By combining the two models, it became possible to explain the liver cell viability and cell death after TiO_2 NP exposure [11]. Upon exposure, TiO_2 NPs have been recovered in internal organs including the liver. Thus, these NPs are proposed to cause cellular or organ dysfunction in the liver or lungs. TiO_2 NPs may impair insulin responses in liver-derived cells, either by inflammatory activation of macrophages or by directly interfering with insulin signaling. Using Conditioned Medium (CM) approaches and real-time quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), a study revealed that exposure to TiO_2 NPs activates macrophages' expression of TNF-α, IL-6, IL-8, IL-1α and IL-1β and the resulting CM induces insulin resistance in Fao cells. Furthermore, direct exposure of Fao cells to TiO_2 resulted in activation of the stress kinases p38MAP kinase and JNK. It also resulted in the induction of insulin resistance at the metabolic as well as signaling levels. The result showed that man-made NPs may induce an endocrine abnormality which is the root cause of some of the most common human diseases which can lead to insulin resistance in liver-derived cells [12].

Studies related to hepatotoxicity on rat models

One of the studies investigated the toxic effects of TiO_2, ZnO and Al_2O_3 NPs on mouse brain, erythrocytes and liver. A single oral dose of 500 mg/kg of each nanoparticle was administered to male mice for 21 successive days. The results suggested that exposure to nano-metallic particles produced a significant oxidative stress in erythrocytes, liver and brain; and induced toxic manifestations. The toxic effects produced by these nanoparticles were more pronounced in the case of zinc oxide, followed by TiO_2 and Al_2O_3 NPs [2]. The signaling pathway of inflammation of the mouse liver caused by intra-gastric administration of TiO_2 NPs was assessed by Toll-Like Receptor-2 (TLR2), TLR-4, IκB Kinase (IKK-α, IKK-β), IκB Nucleic Factor-κB (NF-κB), NF-κBP52, NF-κBP65, Tumor Necrosis Factor-α (TNF-α), NF-κB-Inducible Kinase (NIK), Interleukin-2 (IL-2). The results showed titanium accumulation in liver, histopathological changes, hepatocyte apoptosis and liver function damage. Enzyme-linked immunosorbent assay and qRT-PCR analyses revealed that TiO_2 NPs could significantly increase the mRNA and protein expression of TLR2 and TLR4. These NPs also resulted in increased expressions of several inflammatory cytokines, including IKK1, IKK2, NF-κB, NF-κBP52, NF-κBP65, TNF-α, and NIK. TiO_2 NPs can significantly decrease the mRNA and protein expression of IκB and IL 2. The signaling pathway of liver injury in the TiO_2 NPs-stimu-

lated mouse liver might occur via activation of TLRs→NIK→IκB kinase→NF-κB→TNF α→inflammation→apoptosis→liver injury [13].

Nano-anatase TiO_2 (5 nm) was injected for consecutive 14 days into the abdominal cavity of ICR mice. Inflammatory responses of liver was examined after the injection. ELISA and RT-PCR analyses revealed that nano-anatase TiO_2 can significantly alter the mRNA and protein expressions of various inflammatory cytokines which included macrophage migration inhibitory factor, nucleic factor-κB, tumor necrosis factor-α, interleukin-6, interleukin-1β, cross-reaction protein, interleukin-4 and interleukin-10. The results implied that the nano-anatase TiO_2-induced liver toxicity may involve inflammatory responses and liver injury [14].

Table 2: Studies representing the toxic effects of titanium dioxide nanoparticles on liver

S.No.	Author	Year	Model	Organ	Results	Reference No.
1	Su *et al.*	2018	Human	Liver	Both FeO_3-TiO_2 NPs and TiO_2 NPs may induce oxidative stress and have a potential to pose carcinogenetic effect on human liver	10
2	Laomettachit *et al.*	2017	Human	Liver	Comparison of PBPK and cell response model showed an increase in cell viability and death of liver cells	11
3	Gurevitch *et al*.	2012	Human	Liver	Exposure to TiO_2 NPs induced insulin resistance in liver-derived cells and this caused abnormality in the endocrine system	12
4	Shrivastava *et at.*	2013	Rat	Liver	Exposure to TiO_2, ZnO and Al_2O_3 nano-metallic particles resulted in a significant oxidative stress in erythrocytes and liver; induced toxic manifestations	2
5	Cui *et al*.	2011	Rat	Liver	Titanium accumulation in liver; histopathological changes; hepatocyte apoptosis; and liver function deterioration	13
6	Ma *et al*.	2009	Rat	Liver	Inflammatory responses and liver injury may be involved in nano-anatase TiO_2-induced liver toxicity	14

TiO_2 NPs: Titanium Dioxide Nanoparticles; PBPK: Physiologically-Based Pharmacokinetic

Neurotoxicity

Neurotoxicity is a form of toxicity which involves a chemical, biological or physical agent resulting in an adverse effect on the structure or function of the central or peripheral nervous system. It occurs when the exposure to natural or man-made toxic substances called neurotoxicants alter the normal activity of the nervous system. This can lead to disruption or even killing of the neurons. Neurotoxicity can result from exposure to substances used in radiation treatment, chemotherapy, organ transplants or drug therapies. Symptoms may appear instantly after exposure which can include loss of memory, limb weakness or numbness, loss of vision or intellect, cognitive and behavioural problems, headache; and sexual dysfunction. Certain individuals may be especially vulnerable to neurotoxicants who carry certain disorders.

Studies related to neurotoxicity on rats

A number of studies have evaluated the toxicity of TiO_2 NPs on the central nervous system. In a study, cell cultures were derived from embryonic cortical brain of rats. After 24 to 96 h of incubation with TiO_2 NPs (5 to 20 μg/ml), a significant reduction in neuroblasts was observed. TiO_2 NPs reached the brain through the blood brain barrier after intraperitoneal injection and promoted various histological injuries including cellular lysis, neuronal apoptosis, and inflammation [15]. In another study, ICR mice were injected with various dozes of nano-particulate anatase TiO_2 NPs (5 nm) into the abdominal cavity daily for 14 days to study the mechanisms underlying the effects of these nano moieties on the brain. Results revealed that high-dose of nano-particulate anatase TiO_2 NPs could induce some neurons to turn into filamentous shapes and others into inflammatory cells. Oxidative stress and injury to the brain occurred as nano-particulate anatase TiO_2 NPs appeared to trigger a cascade of reactions such as lipid peroxidation; reduction in activities of antioxidative enzymes, total anti-oxidation capacity, excessive release of nitric oxide, downregulation of acetyl-cholinesterase activity and reduction in glutamic acid [1].

Clastogenicity, genotoxicity, and mutagenicity induced by TiO_2 NPs in mice was found to be reduced by co-administration of the free radical scavenger Chlorophyllin (CHL). In another study, male mice were given multiple injections either of each of three dose levels of nano-sized TiO_2 (500, 1000, or 2000 mg/kg bw/day) alone, CHL (40 mg/kg bw/day) or both simultaneously into the abdominal cavity for 5 consecutive days. It was observed that genotoxicity of TiO_2 NPs was significantly reduced and returned to control level after CHL co-administration. Moreover, CHL administration significantly reduced hepatic malondialdehyde levels. It also increased glutathione levels and activities of glutathione peroxidase, superoxide dismutase and catalase. Thus, CHL co-administration normalized the genotoxicity of nano-TiO_2 [16]. TiO_2 NPs may be distributed within the body and get accumulated in the brain, heart, spleen, lung and kidney of mice after intraperitoneal administration. The organ/body weight ratios for the spleen, heart and kidney were significantly elevated whereas for lung and brain were decreased. High doses of nano-TiO_2 significantly damaged the functions of liver and kidney. Exposure also affected lipid and glucose metabolism. TiO_2 NPs ruptured and cracked nerve cells and resulted in inflammatory cell infiltration in the brain. After nano-TiO_2 exposure, the activities of inducible NOS (iNOS), Nitric Oxide Synthases (cNOS) and acetylcholinesterase; and the levels of glutamic acid and nitrous oxide were changed in the brain [17].

Studies related to neurotoxicity using human models

A widespread application of TiO_2 NPs raises the question about safety of their use in the context of potential occupa-

tional, environmental and intentional exposure of humans and biota. The long term exposure to TiO_2 NPs show adverse effects on human health. Transport of ultrafine TiO_2 particles in systemic circulation and further transition through barriers, especially the placental and blood-brain ones, are well documented. Therefore, from the developmental point of view, there is a raising concern in the exposure to TiO_2 NPs during critical windows, in the pregnancy or the lactation period, and the fact that human mothers, women and men in fertile age and last but not least children may be exposed to high cumulative doses [18]. TiO_2 NPs may accumulate in the brain, especially in the cortex and hippocampus as these moities can easily enter the body through inhalation and can cross blood-brain barrier. The TiO_2 NPs exposure resulted in microglia activation, reactive oxygen species production, activation of signalling pathways involved in inflammation and cell death. Consequently, such action led to neuro-inflammation and brain injury [19]. TiO_2 NPs may affect the brain development of embryo by crossing the placental barrier. Cellular components, such as mitochondrial, lysosome, and cytoskeleton, could also be influenced as well. Spatial memory, recognition ability and learning ability of TiO_2 NPs-treated rodents were significantly reduced. These results revealed that accumulation of TiO_2 NPs in the brain could lead to neurodegeneration [20]. Thus, metallic nanoparticles pose a considerable risk [21] to human health and their exposure should be reduced to minimize the health hazards.

Table 3: Studies representing the neurotoxic effects of titanium dioxide nanoparticles

S. No.	Author	Year	Animal used	Organ	Result	Reference No.
1	Valentine *et al.*	2018	Rat	Brain	Exposure to TiO_2 NPs showed reduction of neurons and induced apoptosis and inflammation in rat brain	15
2	Ma *et al*.	2009	Rat	Brain	High-dose nano-particulate anatase TiO_2 NPs could induce some neurons to turn into filamentous shapes and may result in oxidative stress in the brain	1
3	El-Ghor *et al*.	2014	Rat	Brain	Genotoxicity caused by exposure to nano-TiO_2 in the brain was normalized after CHL co-administration	16
4	Jia *et al*.	2017	Rat	Brain	TiO_2 NPs ruptured and cracked nerve cells in the brain; activity of acetylcholinesterase was altered in the brain after nano-TiO_2 exposure	17
5	Rollerova *et al*.	2015	Human	Brain	Exposure of TiO_2 NPs showed effects on the development of the central nervous system	18
6	Czajka *et al.*	2014	Human	Brain	TiO_2 NPs exposure resulted in microglia activation, ROS production, activation of signalling pathways involved in inflammation and cell death	19
7	Song *et al.*	2017	Human	Brain	Accumulation of TiO_2 NPs may lead to dysfunctions of central nerve system and may also cause neurodegeneration	20

Conclusion

Extensive applications of TiO_2 NPs raise the concern about safety of their use in occupational as well as environmental conditions. The present paper reveals the toxic effects of these nano-moieties posed to different organs including lung, liver and brain. After going through the available reports, it was revealed that TiO_2 NPs pose genotoxic and cytotoxic effects in rats and different human cell lines. Rat inhalation experiments have demonstrated the potency of TiO_2 NPs to cause cancers of respiratory tract and lung. Overload was shown to result in oxidative stress and lipid peroxidation; moreover, long term exposures up-regulated the genes involved. Studies also reported TiO_2 NPs to cause reduced cell viabilities, necrosis, apoptosis, endocrine abnormalities and histopathological changes in different organs. Neurotoxic studies reveal reduction in number of neurons and neural inflammation. Conclusively, human exposure to TiO_2 NPs should be minimized so as to reduce the associated health hazards.

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