REVIEW ARTICLE

Current Developments about Titanium Dioxide

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Abstract

Titanium dioxide is the most used colorant in the world. It is used as a food additive (E171) to give food white color. In this review, recent studies investigating the effects of titanium dioxide on health were evaluated. Titanium dioxide can enter the bloodstream and accumulate in some tissues and affect glucose metabolism. Even though studies have shown that titanium dioxide may be cytotoxic and genotoxic, EFSA's latest report states that it is not directly genotoxic or carcinogenic. The acceptable daily intake value (ADI) was not specified, as there are not enough studies on reproductive toxicity. Since health risks are not high enough to be prohibited, they are still used in foods.

Keywords: Titanium dioxide, toxicity, food additive

Introduction

Nanomaterials are defined as substances with specific properties and size smaller than 100 nanometers (Athinarayanan, Alshatwi, Periasamy, & Al-Warthan, 2015). With developing technology, nanomaterials have started to take place frequently in daily life. Titanium dioxide nanoparticles (TiO2 NP), which are food additives, are classified as a nanomaterial containing particles below 100 nanometers (Younes et al., 2019). It is used as a food additive mostly in chewing gums, the almonds, the gel candies, colored beads, in a variety of beverages, sauces, and is used in some white chickpeas. In addition to food additives, it is used in medicine, food supplements, paper industry, textile products, some plastics and many cosmetic products such as sun cream, toothpaste, make-up materials to give white color and brightness (Grande & Tucci, 2016), (Dorier et al., 2017). In the agricultural industry, it is used in the production of fertilizers and pesticides that can significantly affect soil fertility, plant growth, and crop yield (Baranowska-Wójcik, Szwajgier, Oleszczuk, & Winiarska-Mieczan, 2019).

The use of titanium dioxide was first approved by the United States Food and Drug Administration (FDA) in 1966 and then by the European Union in 1969 by the Food and Agriculture Organization/World Health Organization (FAO/Codex Alimentarius). When used as food coloring, it is labeled E171 in Europe and INS 171 in the US. In other areas, titanium white is also called Pigment White 6 or CI 77891 (Ropers, Terrisse, Mercier-Bonin, & Humbert, 2017).

Titanium dioxide nanoparticles are the most widely used pigment in the world, with an annual consumption of 4 million tons (Winkler, Notter, Meyer, & Naegeli, 2018a). Some of the recent results of the studies have raised concerns about possible harm to human health. Therefore, in recent years, many scientific studies have been conducted on the effects of titanium dioxide on health. In this article, titanium dioxide exposure and its metabolism in the body will be discussed, and then-current researches on its toxic effects will be compiled.

Titanium Dioxide Exposure and Metabolism

Titanium dioxide nanoparticles are insoluble in water, organic solvents, hydrochloric acid, and dilute sulfuric acid. As well as being highly resistant to heat, they are not affected by food processes. Besides being resistant, they are also insoluble to low pH in the stomach (Winkler et al., 2018a). Because of this, it can reach the intestines and pass into the bloodstream. Although the whole metabolic pathways of titanium dioxide are not known, nanoparticles have been shown to cause oxidative stress and cell toxicity. In a study investigating the metabolic effects of titanium dioxide on HaCaT human keratinocyte cells, 268 biochemical metabolites, most of which were associated with cellular stress response, were detected, and 85 of them were found to be significantly altered (Tucci et al., 2013).

In the United States, the FDA authorized 1% by weight of food as a colorant, and in the European Union, it is quantum satis which is allowing the usage up to the smallest amount in which the desired effect can be achieved (Winkler, Notter, Meyer, & Naegeli, 2018b). Since there is insufficient information on reproductive toxicity, the acceptable daily intake value (ADI) as a food additive could not be determined (Younes et al., 2018).

Titanium dioxide is taken orally, through the skin and through the respiratory tract, into the bloodstream, and then some of them accumulate in the tissues. When the presence of titanium dioxide in 15 liver and 15 spleen samples donated by people aged 56-104 for use in scientific studies was examined, more than 24% of the titanium dioxide was found to be nano-sized. Although the amount of titanium dioxide deposited was within safe limits in the spleen, it was found to be above the safe limits in the liver (Heringa et al., 2018).

When taken with food, adults are exposed to about 1 mg/kg a day, and children are exposed to more titanium dioxide because of confectionery (Weir, Westerhoff, Fabricius, Hristovski, & Von Goetz, 2012). When 100 mg of titanium dioxide is given orally to volunteers with avarage intestinal permeability, it was determined that it reached the highest level in the blood at the 6th hour (Pele et al., 2015).

Skin exposure to titanium dioxide occurs through cosmetic products. There was no visible deposition on the skin of hairless rats exposed to titanium dioxide for 8 weeks, but deposition occurred in other layers of the epidermis. It was stated that titanium dioxide does not penetrate other organs except the lung and that the nanoparticles in the lung may be passed through respiration (Adachi, Yamada, Yoshida, & Yamamoto, 2013).

Cytotoxic and Genotoxic Effects

Previous studies have found evidence that titanium dioxide causes changes in testosterone levels, testicular functions, and testicular structure by intragastric/intraperitoneal/intravenous practices. Rodríguez-Escamilla et al. investigated the effect of orally administered 5 mg/kg titanium dioxide on testicular structure and impacts on the blood-testicular barrier in BALB/c mice. The results showed that the infiltration of inflammatory cells in the seminiferous tubules was disrupted with the disruption of the blood-testicular barrier (Rodríguez-Escamilla et al., 2019).

In another study, it was observed that by injecting titanium dioxide nanoparticles in pregnant mice, the nanoparticles passed to the placenta, liver, and brain of the fetus. In the same study, it was shown that on the 7th day of fertilization of chicken embryos, food-borne nanoparticles did not cause toxic effects as a result of exposure to different nano-sized food, biomedical, and industrial origin nanoparticles (Freyre-Fonseca et al., 2018).

When fruit flies were given a titanium dioxide (E171) suspension of 0.014 mg/mL for 20 generations, a change in healthy growth and reproductive dynamics, decreased reproduction after repeated reproduction, increased genotoxicity, the emergence of abnormal phenotypes and so on were observed (Jovanović et al., 2018). In a study where the metabolic and cell toxicity activation of micro-sized titanium dioxide was investigated, metastatic melanoma cells were given titanium dioxide at different times (2, 24 and 48 hours) and doses (250 µg/mL, 125 µg/mL, 50 µg/mL, 20 µg/mL, 10 µg/mL, and 1 µg/mL) ≤5 µm.As a result, it was observed that the metabolic activity of melanoma cells decreased, and cell toxicity increased significantly, especially at the highest 2 doses (Zdravković, Zdravković, Lunder, & Ferk, 2019).

In a study by Jensen et al. investigating the effects of titanium dioxide on vasomotor responses, subcutaneous arteries isolated from excess tissues in the abdominal region of bariatric surgery patients were exposed to titanium dioxide at doses of 14 or 140 µg/ml for 30 minutes and 18 hours.As a result of the study, vasomotor dysfunction was observed in human arteries as in previous studies on mice (Jensen et al., 2018).Female Zucker rats were exposed to low-dose (50 mg/kg/week) and high-dose (500 mg/kg/week) titanium dioxide by the intragastric route. As a result of the study, telomere shortening in the lungs and reduction of expression of intestinal tight ligation proteins were observed in both groups (Jensen et al., 2019).

There is some evidence that titanium dioxide can be cytotoxic and genotoxic in different experimental models. However, the European Food Safety Authority (EFSA) evaluated all studies and reported that titanium dioxide had no definite genotoxic effect due to various limitations in these studies (Agency & Health, 2019).

Relationship with Cancer

DNA damage has a central role among cancer-causing factors in all organisms (Basu, 2018). Researches are available that titanium dioxide can cause DNA damage and may have tumor-stimulating effects. In the study of BALB/c male mice, the ability of titanium dioxide to induce DNA damage *in vitro* and to facilitate the *in vivo* growth of colorectal tumors was studied (Urrutia-Ortega et al., 2016).

When gene expression was examined from colon samples which were taken from BALB/c mice after 2, 4, 7 and 21 days exposure at a dose of 5 mg/kg per day, it was concluded that titanium dioxide affects oxidative stress by affecting prostaglandin metabolism and vitamin D pathways (Proquin, Jetten, Jonkhout, Garduño-Balderas, Briedé, de Kok, et al., 2018). To support the results of this study, rats were given titanium dioxide with azoxymethane (AOM)/dextran sodium sulfate (DSS) at the same dose and duration. Changes were observed in cancer signaling pathways, hemostasis, and protein metabolism after 21 days (Proquin, Jetten, Jonkhout, Garduño-Balderas, Briedé, De Kok, et al., 2018).

Mitochondrial membrane damage was observed as a result of exposure to different doses of titanium dioxide to human mesenchymal stem cells for 24 hours, which may be related to the pathophysiology of cancer, diabetes, and obesity (Athinarayanan et al., 2015).When human intestinal Caco-2 cells were exposed to titanium dioxide at 3 - 1000 µg/mL for 24 hours, it was found that free oxygen radicals (ROS) associated with cell toxicity were significantly increased at doses over 125 µg/mL(Hwang, Yu, Kim, Oh, & Choi, 2019).In a study conducted by Bettini et al. on Wistar rats, 10 mg/kg intragastric titanium dioxide was given daily for 7 days. As a result of the study, it was found that titanium dioxide

affects intestinal and systemic immune balance, initiates preneoplastic lesions in the colon, and promotes the development of aberrant crypts (Bettini et al., 2017).

When Caco-2 and Caco-2/HT29-MTX cells were exposed to 10 to 50μg/mL titanium dioxide continuously or 3 times a week for 3 weeks, oxidative stress and DNA damage were seen in both cell types compared to the control group.It has been reported that more cellular response is seen in continuously exposed cells compared to the acutely exposed cells (Dorier et al., 2017). Titanium dioxide leaking into the trachea of male rats at doses of 0.5, 5, 50, 1.5, 15, 150 mg/kg twice a week has been shown to affect the immune system, as well as to cause structural changes in lung and liver tissue (Suker & Jasim, 2018).

The World Health Organization's International Agency for Research on Cancer (IARC) has classified Group 2B carcinogenic (probably carcinogenic to humans) given studies of exposure to titanium dioxide by inhalation (Skocaj, Filipic, Petkovic, & Novak, 2011). However, the current EFSA report states that more and more long-term studies are needed to make a definitive judgment on the carcinogenic effect of titanium dioxide (Agency & Health, 2019).

Effects on Central Nervous System

The central nervous system, consisting of the brain and spinal cord, is one of the most critical systems in charge of managing important events in the body, handling, processing and storing external information, and commanding and controlling all our behaviors. Titanium dioxide can reach the central nervous system through the bloodstream and the nasal passage by crossingthe blood-brain barrier. Titanium dioxide nanoparticles with the advantage of being nano-sized or low molecular weight can cross the blood-brain barrier which protects the system from harmful chemicals to maintain normal functions of the central nervous system in a healthy way (Song, Liu, Feng, Wei, & Shao, 2015).

When the common results of respiratory and intranasal exposure studies in experimental animals are examined, it is seen that titanium dioxide can accumulate in the brain and increase oxidative stress. In 3 different studies conducted by Ze et al., mice were exposed to titanium dioxide in size of 5-6 nm and doses of 2.5 mg, 5 mg, and 10 mg/kg intranasally for 90 days. In the first study, accumulation in the brain and an increase in oxidative stress, which was caused by the activation of the P38-Nrf2 signaling pathway, was observed (Y. Ze et al., 2013). In the second study, accumulation in the brain, increased oxidative stress, increase in all glial cells and tissue necrosis were observed (Y. Ze, Hu, et al., 2014). In the last study, it was observed that titanium dioxide accumulates in the hippocampus and causes lesions, excessive proliferation of all glial cells, changes in gene expression of proteins and proteins involved in signaling pathways, neuroinflammation and spatial memory disturbances (Y. Ze, Sheng, et al., 2014).

In another study that examined intranasal exposure for 9 months, it was seen that when 5-6 nm titanium dioxide was given at doses of 1.25 mg, 2.5 mg and 5 mg/kg, it resulted with increasing glutamate release and phosphatized glutaminase activity in the hippocampus and decreasing glutamine and glutamine synthetase in the hippocampus. As a result, it was found that titanium dioxide affects glutamate metabolism (X. Ze et al., 2016).

In studies investigating the effects of titanium dioxide on memory and behavior, it was concluded that nanoparticles accumulate in the hippocampus and cause apoptosis, which may be associated with learning and short-term memory in mice. In addition, it has been reported that the risk of schizophrenia, depression, attention deficit, and hyperactivity disorder and anxiety disorder increases as neurotransmitters reduces as a result of titanium dioxide accumulation in the brain (Hu et al., 2011).In a similar study, passive behavior, loss of appetite, tremor, and latergia were observed in adult rats exposed to different nanoscale titanium dioxide nanoparticles for 2 days (J. Chen, Dong, Zhao, & Tang, 2009). In another study by Cui et al., Pregnant mice were injected with titanium dioxide on days 6, 9,

12, 15, and 18 of pregnancy. Brain cell samples were taken from the offspring of mice on the 2nd day of birth. It was found that nanoparticles in cell samples caused oxidative stress in the hippocampus by decreasing antioxidant enzymes in the brain. As a result of the behavioral test, which was performed on the 40-43th days of adulthood, passive and depressive behaviors were observed in the offsprings (Cui et al., 2014).

As a result of the Morris Water Maze Test and Passive Avoidance Test applied between adult rats exposed to and without exposure to titanium dioxide in the womb, there was a significant decrease in learning and memory in the exposed group (Mohammadipour et al., 2014). In another study that examined the results of exposure in the womb, sociability, and repetitive behavior tests were performed. The results of the study showed a decrease in the time spent with other mice with the increase indoses(Notter et al., 2018).In mice exposed to 10, 25, and 50 mg/kg titanium dioxide for 45 days, it was found that the number of tyrosine hydroxylase neurons was significantly reduced in mice treated with 25 mg and 50 mg doses compared to those receiving 10 mg. It has been reported that damage caused by dopaminergic neurons may cause Parkinson's disease (Heidari, Mohammadipour, Haeri, & Ebrahimzadeh-bideskan, 2019).

Effects on Glucose Metabolism

In the study, the effect of titanium dioxide on blood glucose levels was examined. When 64 mg/kg titanium dioxide was given orally to rats daily, it was observed that the amount of free oxygen species and blood glucose did not change. Besides, there were no histopathological changes in the organs regulating plasma glucose homeostasis (Gu et al., 2015).In a study by Chen et al. on rats, rats were exposed to titanium dioxide at doses of 0, 2, 10, and 50 mg/kg per day for 30 and 90 days.As a result of the study, it was reported that titanium dioxide may cause hypoglycemic effect by decreasing the absorption of glucose from intestines and increasing hepatic glucose metabolism (Z. Chen et al., 2018).

In a study investigating the effects of titanium dioxide during pregnancy, rats were given 5mg/kg titanium dioxide nanoparticles daily from day 5 to day 18 of pregnancy. As a result of the study, it was observed that maternal blood glucose levels increased, and microbiota changed. However, it cannot be concluded that the change in microbiota is due to titanium dioxide exposure or the natural outcome of the gestational process (Mao et al., 2019).In a study of pancreatic tissues from eight Type 2 diabetic and 3 non-diabetic subjects, titanium dioxide was found to accumulate only in Type 2 diabetic tissues. Based on the results of this preliminary study on pancreatic tissue, it has been suggested that Type 2 diabetes and other diseases associated with pancreatic inflammation may be related tonano-size titanium dioxide crystals (Heller, Jarvis, & Coffman, 2018).

Effects on Microbiota

Microorganisms, which make up the majority of microbiota and live in the gastrointestinal tract, have an important role in human health by affecting many physiological functions in the body. It is thought that titanium dioxide and other nanomaterials can cause colitis, obesity, diabetes, and other diseases by causing the death of microorganisms forming microbiota or by affecting their functions (Pietroiusti, Magrini, & Campagnolo, 2016). In a study of Sprague-Dawley rats, rats were orally exposed to titanium dioxide at a dose of 0, 2, 10, 50 mg/kg in size of 29 ± 9 nm. In the study, it was found that titanium dioxide exposure caused subtantial changes in colon morphology, and also 25 metabolites and aminoacyl-tRNA biosynthesis caused significant changes in the metabolic pathway. As a result, it was stated that titanium dioxide taken orally can cause intestinal microbiota and intestinal related metabolic disorders in vivo (Z. Chen, Han, Zhou, Zhou, & Jia, 2019).

The *in vitro* Human Gastral Simulator (HGS) system, which was formed by a sample of intestinal microbiota from three male volunteers, was exposed to 100 mg/day titanium dioxide. As a result of the study, it was concluded that the direct effect of titanium dioxide on human intestinal microbiota was limited due to the absence of significant changes in the production of short-chain fatty acids (Agans, Gordon, Hussain, & Paliy, 2019).In a study by Mu et al., The 0.1% titanium dioxide diet, the amount of exposure in individuals, was administered to mice for 3 months. It has been reported that long-term dietary intake of titanium dioxide affects the balance of the intestinal flora and the immune system and may also cause intestinal inflammation and threaten health (Mu et al., 2019).

In the study where Pinget et al. investigated the effects of titanium dioxide on microbiota, mice exposed to 50 mg of titanium dioxide showed an increase in macrophages, cytokines, and T cell response. The study showed a significant reduction in short-chain fatty acids, and it has been commented that the decrease in the protective acetate may increase the risk of diabetes, asthma, food allergy, and colorectal cancer (Pinget et al., 2019).

In the study where male C57BL/6 mice were given 100 mg of titanium dioxide daily for 28 days to investigate changes in microbiota, fecal samples were taken from mice 2 hours after titanium dioxide consumption each week. As a result, it was observed that titanium dioxide did not affect the intestinal microbiota diversity, but it caused changes in the number of some bacterial species. It was also shown that titanium deposited in the spleen, lungs, and kidneys had no significant effect on organ histology. The researchers stated that chronic consumption of foods containing titanium dioxide may lead to intestinal dysbiosis and cause severe toxic effects on the gastrointestinal tract (Li et al., 2018).

Intestinal microbiota from healthy subjects was exposed to 3 mg/L titanium dioxide for 5 days. As a result, titanium dioxide caused changes in microbiota phenotype such as cell size, cell concentration, sugar and protein content of extracellular polymeric material, amount of short-chain fatty acids. The effects of titanium dioxide on the phenotype of the microbial population have been shown to cause significant non-lethal changes (Taylor, Marcus, Guysi, & Walker, 2015).In a study by Dudefoi et al. on human intestinal ecosystem culture, cell culture was exposed to titanium dioxide as a food additive (100 to 250 mg/L) for 48 hours. The study showed that titanium dioxide had only a small effect on gas production and fatty acid profile. In general, it has been noted that titanium dioxide does not significantly alter human intestinal microbiota, but it cannot be conclusively concluded that the cumulative effects and higher concentrations of chronic uptake are not significant toxicity to our microbiome (Dudefoi, Moniz, Allen-Vercoe, Ropers, & Walker, 2017).

Conclusion

Titanium dioxide is the most widely used pigment in the world. As consumption is increasing day by day, interest in the possible effects on human health has also increased. Some studies have shown that this pigment can affect microbiota, accumulate in tissues by participating in blood circulation, cause some biochemical changes in the body, and affect memory and behavior. EFSA has re-evaluated the toxicity studies of titanium dioxide in recent years and reported that it is not directly genotoxic or carcinogenic, but its *in vitro* genotoxic effect is due to a secondary mechanism that causes oxidative stress. In this report, although the effect of titanium dioxide on telomere length, which is known to be related to DNA stability, is statistically significant, it is stated to have a small and uncertain biological significance (Agency & Health, 2019). Current studies on titanium dioxide will be evaluated at regular intervals, and it will be decided whether to change the codex regulation or not. If the health risks do not exceed a certain limit, and no decision is made to remove it, the use of this additive will continue. However, consumers may avoid this additive because of some possible adverse effects.

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