SCHOLASTIC:
Journal of Natural and Medical Education
Volume 2 Issue 5, Year 2023 ISSN: 2835-303X
https://univerpubl.com/index.php/scholastic

Asessment of the Intake of Titanium Dioxide into the Body with Food

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Article Information

Received: March 25, 2023
Accepted: April 26, 2023
Published: May 27, 2023

Keywords: *E171- TiO_2 adverse health effects; food supplement; food safety; mode of action; nanoscale; nanomaterial; oral exposure; review; titanium dioxide; toxicity.*

ABSTRACT

Titanium dioxide (TiO_2) is used as a food additive (E171) and can be found in sauces, icing and chewing gums, as well as personal care products such as toothpaste and pharmaceutical tablets. Along with the ubiquitous presence of TiO_2 and recent awareness of its potentially hazardous properties, there are concerns about its use in commercially available products.

Especially the nano-sized (<100 nm) fraction of TiO_2 requires a more detailed assessment of potential adverse health effects after ingestion. A workshop organized by the Dutch Risk Assessment and Research Office (BuRO) highlighted uncertainties and gaps in knowledge regarding TiO^2 absorption in the gastrointestinal tract, its distribution, potential for accumulation and induction of adverse health effects such as inflammation, DNA damage and tumor development. The purpose of this review is to identify and evaluate recent toxicological studies of dietary TiO_2 and nanosized TiO^2 in ex vivo, in vitro and in vivo in gastrointestinal experiments, and to postulate an adverse outcome pathway (AOP) after ingestion. In addition, this review summarizes the recommendations and results of the Bureau's 2018 expert meeting to provide input to the hazard identification and risk assessment process for TiO_2 ingress.

Introduction

In the process of innovative development of the food industry and improvement of food production technology, the role of food additives is increasing.The widespread use of food additives is justified by the fact that food products are transported over long distances, some of them are perishable. The introduction of additives into their composition is accompanied by an increase in the shelf life. Also, consumer preferences are reduced to the attractive appearance of the finished product, low cost, ease of use of semi-finished products, good taste.

Titanium dioxide (TiO_2) is a widely used white pigment and opacifier used in paints, pharmaceuticals, cosmetics, and food [1]. When used as a food additive in the European Union (EU), it is listed as E171 to refer to a special food form of TiO_2 that has no nutritional value and is used to impart white color, tint to other pigments, or in pharmaceuticals [2].Whitening is best achieved with TiO_2 particles in the 200–300 nm size range due to their light scattering effects. TiO_2 occurs naturally in three different crystal structures - anatase, rutile and brookite, but only anatase and rutile are allowed as a food additive. The European Union allows E171 (anatase and rutile in uncoated forms, no surface treatment) in quantity (no limit) based on its low absorption and subsequent low toxicity, perceived inertness and low solubility [3].However, its low toxicity and inertness are debated, as long-term inhalation studies over two years have shown the development of lung tumors in rats after exposure to high concentrations of $TiO._2$ As a result of these findings, the International Agency for Research on Cancer (IARC) has classified TiO_2 as

"possibly carcinogenic to humans after inhalation" [4].In 2017, the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) published an opinion proposing that TiO_2 be classified as a category 2 carcinogen after inhalation in accordance with the criteria of the Classification, Labeling and Packaging Regulation (CLP) [5].On February 18, 2020, the EU took into account the opinion of the ECHA and published the classification of TiO_2 as a suspected carcinogen (category 2) by inhalation in the form of a powder containing at least 1% of particles with an aerodynamic diameter of 10 μm in accordance with the CLP Regulation (EC No. 1272/2008). The classification will apply from 1 October 2021 after an 18-month transition period [6]. It is not yet clear what the observed toxicity and post-inhalation hazard classification for oral toxicity mean.

In recent years, a growing body of research has examined the behavior and effects of E171 and nanosized TiO_2 after ingestion and has found potential side effects including induction of inflammation, generation of reactive oxygen species (ROS), and cogenotoxicity. effects [7].Subacute and subchronic studies have also revealed the induction of epithelial hyperplasia and premalignant lesions in the colon of rats and mice after administration of E171, while other oral toxicological studies have not confirmed such effects [8].For the oral dietary supplement E171, the European Commission requested a re-evaluation of TiO_2 by the European Food Safety Authority (EFSA) following the publication of the ANSES studies in 2017. EFSA concluded that the results of these studies are not worthy of attention. a rediscovery of existing opinion, but it is proposed to fill existing data gaps, reduce uncertainty, and carefully evaluate new results regarding their adverse effects and the physicochemical properties of the TiO_2 particles used [9].The focus of oral exposure to TiO_2 assessment should potentially be extended from dietary supplement E171 to personal care products, packaging and coating of household items [10]. Daily dietary intake of E171 can reach several hundred milligrams, of which at least 10–40% is in the form of TiO_2 nanoparticles.Long-term exposure to such amounts of nano- and micro-sized TiO_2 raises concerns about the risk of potential accumulation in organs and potentially harmful effects on human health. Human studies with oral administration of TiO_2 have shown low bioavailability. Basal blood levels of titanium ranged from 5.0–11.8 μg/L (average 11.1 μg/L) and peaked after 8–12 hours at 37. 4-49.7 μg/l after oral administration of 24.7 mg TiO_2 in a gelatin capsule.The introduction of 380 nm TiO2 (anatase) showed lower absorption than 160 nm TiO_2 (anatase). The highest blood titanium concentration was found at 104.6 μg/L after ingestion of 45.8 mg TiO_2 in a gelatin capsule 8 hours later, indicating a large difference in absorption among a group of six male volunteers. Ingestion of 100 mg of dietary TiO_2 (E171) increased total blood titanium levels after 6–8 hours, with peak blood titanium concentrations reaching 14 ppb compared to a baseline level of 1.5 ppb.

Contrary to these findings, studies that used TiO_2 of different sizes did not show statistically significant TiO_2 post-absorption. Although the absorption of ingested TiO_2 across the healthy intestinal barrier appears to be very low, it is important to take into account factors such as the net volume of translocated particles across the intestinal barrier., a possible disruption of intestinal barrier function that promotes translocation and bioaccumulation of TiO_2 particles. in systemic organs, with an accurate assessment of potential health hazards.

Hering et al. (2016) and Rompelberg et al. (2016) published a review of studies studying the absorption of TiO_2 nanoparticles. Following their physiological pharmacokinetic (PBPK) modeling, these investigators concluded that TiO_2 nanoparticles could be absorbed, albeit at a very slow rate of approximately 0.02 to 0.05%. Translocation to the lymphatic system and bloodstream can lead to the deposition of TiO_2 nanoparticles in tissues and organs after ingestion.TiO_2 deposition has been observed in Peyer's patches in humans, especially in patients suffering from inflammatory bowel disease (IBD). Regardless of the degree of TiO_2 absorption, a significant amount of TiO_2 (approximately 99%) remains and accumulates in the intestinal

lumen before it is excreted in the feces, without any changes or metabolism [11].Due to accumulation in the intestinal lumen prior to excretion, interactions of TiO_2 with the gut microbiota are possible, which can lead to changes in gut homeostasis and possibly affect the health of the host.After reviewing the literature on the potential risks of oral exposure to TiO_2, we conclude that the current body of evidence raises human health concerns regarding long-term ingestion of E171. Widespread human exposure, combined with reports of neoplastic and pro-inflammatory responses in animal experiments, points to the need to fill identified knowledge gaps that are critical in the hazard identification and risk assessment process.

Children are of particular concern due to their proportionately higher TiO_2 intake, as well as IBD patients given their potential risk of increased absorption due to impaired gut health. Animal experiments have shown that chronic exposure to E171 can lead to translocation and bioaccumulationTiO_2 through the bloodstream to various organs including the liver, kidneys, placenta and brain. In various types of models, gene expression patterns have been reported that are associated with inflammation and tumor development. Experiments in vivo, ex-vivo and in vitro, mainly carried out with TiO_2 nanoparticles,show that TiO_2 can lead to the formation of ROS, which is associated with the induction of genetic damage, the initiation and stimulation of inflammation and the stimulation of tumor formation. Endocrine and reprotoxic effects found in rodent studies indicate the need for more research to reduce uncertainties.These complex interplays of molecular mechanisms, including local persistent inflammation, oxidative-antioxidant imbalance, immunosuppression, apoptosis, alteration of microbial health, and pathways associated with colon cancer, need to be further explored in order to better understand the molecular biological process, their interaction and involvement after chronic exposure to E171.The workshop noted that in vitro studies of chronic carcinogenicity in animals may have limitations in determining the impact on the incidence of rare tumors, such as colon cancer in rats.To this end, specific disease models can provide additional information. In addition, it was concluded that the correct characterization of TiO_2 particles is critical for future studies, and that the type of crystal form and particle size used, both in commercially available E171 and in experimental toxicity studies, should be well described.With oral exposure to TiO_2 through drinking water (oral via gavage) and diet, the effect of the food matrix on bioavailability and adverse health effects is still poorly understood and could potentially affect the properties and toxicokinetics, therefore, when identifying the E171 hazard.

Finally, studies of dietary interventions in humans are needed to demonstrate or refute adverse reactions to E171 under appropriate exposure conditions, as well as to better understand the potential cellular and molecular mechanism of action in humans.

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