

August 29, 2023

Via Electronic Submissions via Regulations.gov

Division of Dockets Managements (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1030
Rockville, MD 20852

Re: Docket No. FDA-2023-C-1487 for "Filing of Color Additive Petition from Environmental Defense Fund, et al.; Request to Revoke Color Additive Listing for Use of Titanium Dioxide in Food" (88 Fed. Reg. 27818-19)

Dear Sir/Madam,

The Consumer Healthcare Products Association ("CHPA") serves as the leading national trade association representing manufacturers and distributors of over-the-counter drugs and dietary supplements. Our association is deeply committed to upholding the highest levels of safety in the manufacturing of dietary supplements. Thus, we appreciate this opportunity to express our strong opposition to the proposed repeal of 21 CFR 73.575, which currently permits the use of titanium dioxide (TiO₂) in food and dietary supplements.

An overwhelming consensus from reputable regulatory authorities and scientific bodies strongly contradicts the hasty conclusion made by the European Food Safety Authority (EFSA) regarding the safety of TiO₂. There is a substantial body of scientific evidence that has been extensively reviewed by a diverse set of regulatory authorities that supports the safe use of TiO₂ as a food additive. Dismissing this extensive evidence and adopting EFSA's precautionary approach without scientific justification would disregard the wealth of accumulated scientific research spanning several decades. These comments aim to summarize the available information to reinforce the safety of TiO₂ as a vital component in food products.

The proposed action has raised significant concerns within our industry, as it carries potential consequences that extend beyond our immediate scope. Product quality, consumer choice, and the economic viability of our businesses could be affected if this regulation is repealed. We believe it is important to carefully consider the implications of repealing 21 CFR 73.575 before making any decisions that may compromise the safety and well-being of consumers.

TiO₂ has been safely utilized in the food and dietary supplement industry for several decades. TiO₂ is a mineral widely used as a food additive and coloring agent, and has recently come under scrutiny, with calls for its ban due to potential health concerns. While it is important to prioritize consumer safety, we are deeply concerned that the current narrative being advanced does not accurately reflect the balance of scientific evidence relating to the safety of TiO₂ when used as a food additive.

CHPA members strive to ensure that consumers have access to safe and reliable healthcare products. We believe that maintaining this regulation is crucial to upholding quality standards for many products currently on the market. TiO₂ is required to be listed on dietary supplement labels, which enables consumers to make informed choices about the products they purchase and consume. A hasty ban on TiO₂ in dietary supplements would have far-reaching consequences. TiO₂ plays a crucial role in enhancing the stability and functionality of various dietary supplement finished products. Our response aims to provide a comprehensive perspective, highlighting the importance of maintaining the allowance of TiO₂ and addressing the concerns raised.

1. Established Safety and Regulatory Compliance

The safety of TiO₂ has been extensively evaluated by leading scientific organizations and regulatory agencies around the world, including the U.S. Food and Drug Administration (FDA), Food Standards Australia New Zealand (FSANZ), Health Canada, Food Standards Scotland (FSS), and the Food Standards Agency (FSA) and Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. For example, In March 2022 following a thorough review, the UK Committee on Toxicity of Chemicals in Food of the UK Food Standards Agency disagreed with the negative EFSA opinion considering that the weight of evidence did not support the conclusions. The FSA concluded that there are no identified safety issues, consequently indicating no need for regulatory changes in England and Wales. Similarly, neighboring FSS arrived at the same conclusion after their evaluation of the available evidence. The FSA considered that the EU conclusion was highly risk adverse and based on weak scientific evidence and instead set guidelines regarding the maximum allowable levels of TiO₂ in food and dietary supplements, ensuring its safe consumption.

In June 2022, Health Canada published a State of the Science report¹ on TiO₂ as a food additive. This review found there is no conclusive scientific evidence that TiO₂ in food is a concern for human health.

In September 2022 FSANZ completed a Review of the Safety of Titanium Dioxide² as a food additive. The FSANZ review concluded there is currently no evidence to suggest dietary exposure to food-grade TiO₂ is a concern for human health.

¹ Health Canada. Titanium Dioxide (TiO₂) as a food additive: current science report. Available at: <https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/titanium-dioxide-food-additive-science-report.html>

² Food Standards Australia New Zealand. Review of Titanium Dioxide as a Food Additive. Available at: <https://www.foodstandards.gov.au/consumer/foodtech/Pages/Review-of-titanium-dioxide-as-a-food-additive.aspx>

In January 2023, The FDA communicated to the Titanium Dioxide Manufacturers Association (TDMA)³ that it reviewed the findings of EFSA's 2021 Opinion on TiO₂. The FDA notes that EFSA's 2021 Opinion continued to confirm no general and organ toxicity, as well as no effects on reproductive and developmental toxicity. In its 2021 Opinion, EFSA noted that it could not rule out genotoxicity and included genotoxicity tests on TiO₂ nanomaterials. Some of the genotoxicity tests included test materials not representative of the color additive, and some tests included administration routes not relevant to human dietary exposure. The available studies do not demonstrate safety concerns connected to the use of TiO₂ as a color additive. The FDA continues to allow for the safe use of TiO₂ as a color additive in foods generally according to the specifications and conditions, including that the quantity of TiO₂ does not exceed 1% by weight of the food, found in FDA regulations at 21 CFR 73.575.

Numerous scientific studies have consistently reaffirmed the safety of TiO₂ within the regulatory limits established by 21 CFR 73.575. Repealing this regulation based on unsubstantiated safety concerns would disregard the wealth of scientific evidence accumulated over decades.

TiO₂ is commonly considered a poorly soluble low toxicity particulate material of significant socioeconomic importance. It predominantly exists in commerce as surface-modified particle-types. There is an ongoing discussion regarding the influence of surface modifications on the toxicity of TiO₂ materials and how alterations in physical-chemical properties of surfaces impact toxicity.

In a 2019 review, the effect of surface modifications on the pulmonary and oral toxicity of commercial TiO₂ particles was evaluated, with a focus on in vivo studies that included appropriate controls. These studies compared both surface-modified and untreated materials. Notably, two oral toxicity studies were conducted, one using surface treated TiO₂ particles (OECD 408) and the other with untreated TiO₂ particles (OECD 407). The results indicate that there was no adverse impact on toxicity with the surface-coated material. Both studies showed no adverse effects, even at the maximum limit doses that were tested.⁴

The request to revoke the approval of TiO₂ as a food additive has raised concerns regarding the potential risk of nanoparticle absorption and subsequent bioaccumulation in various organs and tissues. This concern stems from the understanding that nanoparticles, particularly those smaller than one hundred nanometers, may bypass the body's natural defenses and enter the bloodstream.

³ TDMA. Jan. 24, 2023. US FDA confirms the safety of titanium dioxide as a food additive. Posted at: <https://www.tdma.info/news/us-fda-confirms-the-safety-of-titanium-dioxide-as-a-food-additive/>

⁴ Warheit DB, Brown SC. What is the impact of surface modifications and particle size on commercial titanium dioxide particle samples? - A review of in vivo pulmonary and oral toxicity studies - Revised 11-6-2018. Toxicol Lett. 2019;302:42-59

Numerous studies examining the fate and behavior of TiO₂ nanoparticles in the body have consistently shown minimal absorption of these nanoparticles with no adverse health consequences.⁵ A 2023 publication by Agaki, et al, provides additional evidence supporting the notion that TiO₂ nanoparticles, when orally dosed, even at limit doses, for 28- and 90-days results in minimal absorption into the lumen of the gut as a normal consequence of oral dosing. In addition, there is minimal absorption into the respiratory tract secondary to oral gavage and possible reflux from the gut, and minimal evidence of submucosal absorption with no evidence of toxicity. There were no systemic adverse health effects observed in the 28-day and 90-day studies, even at maximum limit doses of TiO₂ nanoparticles. The potential genotoxic effect of TiO₂ nanoparticles was evaluated in the liver using micronucleated hepatocytes as a marker for DNA damage. In the study no increase in micronucleated hepatocytes was observed in the liver of males and females dosed with 1,000 mg/kg/bw/day, which does not support the DNA damaging or genotoxic potential of TiO₂ nanoparticles in the liver. In summary, the study by Akagi et al observed no general toxicity, no accumulation of TiO₂ in the kidneys, liver, and spleen, and no evidence of DNA damage even after repeated oral administration of TiO₂ nanoparticles with a crystallite size of 6 nm at doses up to 1000 mg/kg bw/day in male and female rats.

To underscore the safety of dietary supplements as a subcategory of food, this study⁶ used 1,000 mg/kg/bw/day. CHPA conducted an informal survey of its dietary supplement manufacturers and determined the highest TiO₂ content in a typical dietary supplement would be 11,000 ppm, which, as per label recommendations, would result in a daily intake of 14 mg daily. A daily intake of 14 mg in a 70 kg adult is equivalent to 0.2 mg/kg/day. This results in a Margin of Exposure (MoE) of 5,000⁷. A MoE above 100 is considered an acceptable safety margin.

Data generated through standardized testing protocols for toxicity studies generally yield reproducible and reliable results, aiding in establishing safe levels and formulating risk assessments. Three studies⁸ on TiO₂ employed OECD guideline-type oral toxicity tests conducted on rats, evaluating various TiO₂ particles with different sizes and surface coatings. The collective findings from these studies demonstrated the absence of any hazards related to TiO₂, regardless of particle size or surface coating.

⁵ Shi H, Magaye R, Castranova V, Zhao J. Titanium dioxide nanoparticles: a review of current toxicological data. *Part Fibre Toxicol.* 2013 Apr 15;10:15.

⁶ Akagi JI, Mizuta Y, Akane H, Toyoda T, Ogawa K. Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats. *Part Fibre Toxicol.* 2023 Jun 20;20(1):23.

⁷ MoE = NOAEL (1000 mg/kg/day) / 0.2 mg/kg/day = 5,000. Typically, A MoE greater than 100 represents an adequate margin of exposure for food safety.

⁸ Warheit DB, Brown SC, Donner EM. Acute and subchronic oral toxicity studies in rats with nanoscale and pigment grade titanium dioxide particles. *Food Chem Toxicol.* 2015 Oct;84:208-2024.

Summary of the OECD guideline toxicity tests:

90-Day subchronic oral toxicity study in rats:⁹

In this study, male and female rats were given surface coated TiO₂ particles orally for 90 days. The highest dose tested was 1000 mg/kg bw/day, and no adverse effects related to the TiO₂ particles were observed. This led to the determination of a no-adverse-effect level (NOAEL) of 1000 mg/kg bw/day.

28-Day repeated oral dose study in rats¹⁰:

Male rats were orally administered uncoated TiO₂ particles for 28 days. The highest dose tested was 24,000 mg/kg bw/day, and no adverse effects were detected during or after the exposure period. The NOAEL for this study was determined to be 24,000 mg/kg bw/day.

Acute oral toxicity in rats¹¹:

In this study, female rats received a single oral dose of surface treated TiO₂ particles. Doses of up to 5000 mg/kg were tested, and the rats were monitored for 14 days after exposure. The study determined that the oral LD50 (lethal dose for 50% of the rats) for the tested substance was greater than 5000 mg/kg/bw, indicating no significant acute toxicity.

In summary, these three studies, each using different types of TiO₂ particles, consistently showed an absence of adverse toxicological effects.

Studies conducted by the International Agency for Research on Cancer (IARC), have found no evidence to support claims that TiO₂ is carcinogenic when ingested as a food additive.¹² Other studies have evaluated the effect of TiO₂ on gene mutation. In 2022, a thorough assessment was conducted to evaluate the genotoxicity of TiO₂ based on available data. The comprehensive analysis concluded that there is no substantial evidence supporting a direct DNA damaging effect of TiO₂ (both nano and other forms).¹³

2. Manufacturing standards ensure safe use of TiO₂ in dietary supplements

Dietary supplement current Good Manufacturing Practices (cGMPs) provide additional assurances regarding the safe use of TiO₂ in food products. These regulations ensure that only TiO₂ intended for food use, within the limits set by regulatory standards, is utilized. This adds an

⁹ Experimental design methodology for the 90-day subchronic toxicity study (OECD TG 408)

¹⁰ Experimental design methodology for the 28-day repeated-dose study (OECD TG 407)

¹¹ Experimental design methodology for the acute study (OECD TG 425)

¹² International Agency for Research on Cancer (IARC). (2010). IARC Monographs Volume 93: Carbon Black, Titanium Dioxide, and Talc. Retrieved from <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Carbon-Black-Titanium-Dioxide-And-Talc-2010>

¹³ Kirkland D, Aardema MJ, Battersby RV, et al. A weight of evidence review of the genotoxicity of titanium dioxide (TiO₂). *Regul Toxicol Pharmacol*. 2022 Dec;136:105263.

extra layer of consumer safety. Good Manufacturing Practices (GMP) and Hazard Analysis Critical Control Point (HACCP) systems are implemented to monitor and control the production, handling, and use of TiO₂ as a food additive. These practices play a vital role in ensuring the integrity of finished dietary supplements.

Under these practices, thorough verification processes are conducted to confirm the identity, purity, strength, and composition of all components, including TiO₂, used in dietary supplements. This meticulous approach serves to mitigate potential risks associated with the potential misuse of TiO₂ during manufacturing and assures the safety of finished dietary supplements containing this ingredient, providing peace of mind for consumers.

3. Functional Role in Food and Dietary Supplements

TiO₂ serves critical functional purposes in dietary supplements. TiO₂ functions as a stabilizer and opacifier in dietary supplements that provides stability and protects the ingredients from heat, light, and UV exposure. Removing TiO₂ from our formulations would not only impact the aesthetic qualities of these products but also compromise their stability, marketability, and consumer acceptance.

4. Lack of Viable Alternatives

Opponents of TiO₂ argue for the availability of alternative ingredients or production methods. However, the proposed substitutes often fail to replicate the unique properties and functionality that TiO₂ provides. The removal of this ingredient would require extensive reformulation and testing, which would lead to increased costs for manufacturers and potentially reduced consumer choices. Moreover, the use of alternative options may introduce their own set of safety concerns, necessitating thorough evaluation before widespread adoption.

A common alternative to TiO₂ is calcium carbonate. However, using calcium carbonate as a substitute presents its own set of challenges. Firstly, since it is sourced from natural minerals, concerns arise regarding the sustainability of mining practices and their impact on the environment. Additionally, being a natural ingredient, calcium carbonate often contains significant elemental impurities. Meeting the requirements for antacid formulations becomes challenging due to the presence of these impurities. Another point of consideration is that calcium carbonate is an alkaline ingredient. When used in coatings, it can potentially affect the stability of products, especially if the active ingredients are sensitive to pH. These factors collectively demonstrate the complexities and limitations associated with finding suitable alternatives to TiO₂. Furthermore, banning TiO₂ from the US food supply will drive an acute demand for suitable TiO₂ alternatives like calcium carbonate. The heightened demand, resulting from a hasty regulatory change, will stress the available TiO₂ alternative supply and result in increased material costs and material shortages. The U.S. market is still recovering

from post-COVID supply chain disruptions and a ban TiO₂ will only further exacerbate this problem, raise product costs, and threaten availability of affected products for US consumers.

5. Economic Implications

Repealing 21 CFR 73.575 could have significant economic ramifications for the dietary supplement industry. The food and dietary supplement industry relies on TiO₂ as an additive to enhance product aesthetics and stability. Removing TiO₂ would necessitate costly reformulation, product redesign, and new label production causing financial strain on manufacturers and stress to the supply chain as the industry seeks alternatives to TiO₂. In addition, CHPA members market dietary supplements and food supplements internationally, which often requires regulatory submissions and compliance with regulations governing the target country or region. Each country or region may have its own specific requirements for the sale and distribution of dietary supplements, including product registrations and labeling requirements.

Some countries require product registration or notification for dietary supplements with the relevant regulatory authorities before they can be sold. This process often involves submitting detailed information about the product's composition. Replacing TiO₂ with an alternate ingredient would necessitate not only costly reformulation, product redesign, new label production for each country or region individually, it also includes the time and resources needed to complete stability studies, submit data and re-register products around the world.

Furthermore, increased costs could be passed on to consumers, resulting in higher prices for everyday products, including food and supplement items. This only serves to limit opportunities for individuals who rely on dietary supplements to improve and maintain their wellbeing. Furthermore, the potential loss of business and market competitiveness for manufacturers reliant on TiO₂ could adversely impact employment and economic growth.

6. Consumer Perception and Acceptance

Consumers have become accustomed to the presence of TiO₂ in various food and dietary supplement products. Its use has become an industry standard, and consumers often associate its presence with quality, consistency, and safety. Eliminating TiO₂ without scientifically valid justification may lead to altered appearance and stability of products that have been safely consumed for decades. This could result in confusion and mistrust among consumers, as well as resistance to new formulations. Maintaining the status quo allows for the continuity of familiar products and reinforces consumer confidence.

Banning TiO₂ would limit innovation in product development, which would stifle growth and innovation in the food and dietary supplement industries. These industries are important contributors to jobs in the American economy. Without this additive, manufacturers would face significant challenges in developing appealing and high-quality products. The ability to create

innovative and attractive formulations would be severely curtailed, reducing consumer choices and limiting the industry's capacity for growth.

We also underscore the importance of considering the environmental impact. TiO₂ production has been optimized over the years¹⁴, resulting in lower environmental impact. Substituting it may lead to increased environmental costs, in addition to the already high financial burden and quality compromise.

Conclusion

In conclusion, we strongly urge the Food and Drug Administration to deny the petition to repeal 21 CFR 73.575, which permits the use of TiO₂ in food and dietary supplements. While consumer safety is of paramount importance, a knee-jerk ban on TiO₂ in food and dietary supplements would be unjustified. Based on extensive scientific research and regulatory evaluations, TiO₂ is deemed safe for use as a food additive when consumed within established regulatory limits. The safety of TiO₂ as a food additive is evidenced by the lack of significant absorption across the gut, low toxicity, absence of carcinogenicity¹⁵, and lack of evidence demonstrating genotoxicity. Furthermore, its regulatory approval, manufacturing oversight, and industry best practices ensure the responsible use of this ingredient. Continued adherence to these safety measures and ongoing research will contribute to maintaining the safety and integrity of TiO₂ as an essential food additive.

Best Regards,



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¹⁴ Villalobos, M., Cornuault, J., & Roes, A. L. (2019). Environmental impact assessment of titanium dioxide nanoparticles production: a literature review. *Journal of Cleaner Production*, 216, 34-45.

¹⁵ International Agency for Research on Cancer (IARC). (2010). IARC Monographs Volume 93: Carbon Black, Titanium Dioxide, and Talc. Retrieved from <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Carbon-Black-Titanium-Dioxide-And-Talc-2010>