The Challenges in the food industry with the ban of Titanium Dioxide in 2022

A Thesis Presented as part fulfilment for the Award of Master of Science in Food Business Management and Technology by

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Declaration

I, Gabrielle Hortaleza hereby certify that the material, which I now submit for assessment on the programme of study leading to the award of M.Sc., is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of my own work. No portion of work contained in this thesis has been submitted in support of an application for another degree or qualification to this or any other institution.

Signed: Gabrielle Hortaleza **Dated:** 24th April 2023

Gabrielle Hortaleza 24th April 2023

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Abstract

The ongoing human health studies concerning the use of Titanium Dioxide in the food industry has been explored in many literature studies. The European Commission have recently declared a full ban of Titanium Dioxide (E171) as a food and feed additive in the European Union with the six month phasing out period from 07 February 2022 until 07 August 2022 effectively. Following this ban, there is a huge demand for alternatives within the food industry sector and also challenges that comes with this change. The aim of this thesis is to investigate the health implications that TiO_2 has brought about this ban, exploring the alternatives that the food companies have innovated in order to tackle this challenge.

The key findings were that there are many in invo and in vitro studies concerning human ingestion and inhalation however no real human studies completed. The Food industry is continuously innovating on their own portfolio to create a close match to the appearance whitening effect of TiO_2.

In conclusion, there has been a huge progress and response of the companies due to this change, however there is a need to explore further alternatives in the future.

Keywords: Titanium Dioxide Alternatives, Titanium Dioxide Ban, Challenges in the ban of Titanium Dioxide .

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Chapter 1: Introduction

This thesis aims to investigate the evolution of Titanium Dioxide as a food additive and its application in food systems. This thesis will explore how European Food Safety Authority (EFSA) deemed it to be unsafe for consumption in 2021 and later its complete ban in 2022. This thesis will also identify the alternatives for replacing Titanium Dioxide in the current food products as a whitening agent and the challenges that are brought by this change. This paper will also compare these different alternatives as part of the Novelty of this research.

1.1. History of Titanium Dioxide

Titanium Dioxide (TiO_2) is the naturally occurring oxide of Titanium (Ti). It is an odourless, white and non-combustible powder, which holds a molecular weight of 79g/mole, a relative density 4.26 g/cm^3 at 25°C. It also has a high melting point of 1843°C and boiling point of 2972°C. It has been used as white pigment in different applications in food and paints, cosmetics, energy storage, and photocatalysis (Shi *et al.*, 2013; Boutillier, Fourmentin and Laperche, 2022).

The discovery of TiO_2 began by a British mineralogist and clergyman names William Gregor in 1791 in Cornwall whilst analyzing black magnetic sand from Menachan. He was able to produce a metallic white oxide from menachanite mineral ('Titanium Dioxide Pigments', 1983). In 1920, a German chemist called M.H. Klaproth was able to separate TiO_2 from the mineral called rutile, which he named titanium from Greek mythology giants. The first production of pure titanium was produced by an American chemist M.A Hunter in 1910. It was called Ilmenite, which was the ore mineral (Gázquez *et al.*, 2014). Titanium white was first manufactured in France in 1923 as a pigment in its anatase form. In 2017, TiO_2 has been discovered to have a photocatalytic property which then creates a wide variety of applications such as self-cleaning, antibacterial, depollution, and photolysis of water (Jain *et al.*, 2017). There have been different techniques used in the processing of pigment of TiO_2 with nearly 90% of titanium ore available. (Gázquez *et al.*, 2014).

Three crystallographic forms of titanium dioxide occur naturally; anatase, brookite, and rutile (Byranvand *et al.*, 2013). These phases of crystals form an octahedral, with six oxygen that are anions shared by three titanium IV which are cations (Racovita, 2022). The two crystals rutile and anatase form pigments that were used as food additives. (Boutillier, Fourmentin and Laperche, 2022).

There are two ways of obtaining these pigments, one would be by sulfate process using sulphuric acid and by chloride process using chlorine gas which equates to 40% and 60% of the overall TiO_2 production respectively (Gázquez *et al.*, 2014; Ropers *et al.*, 2017)

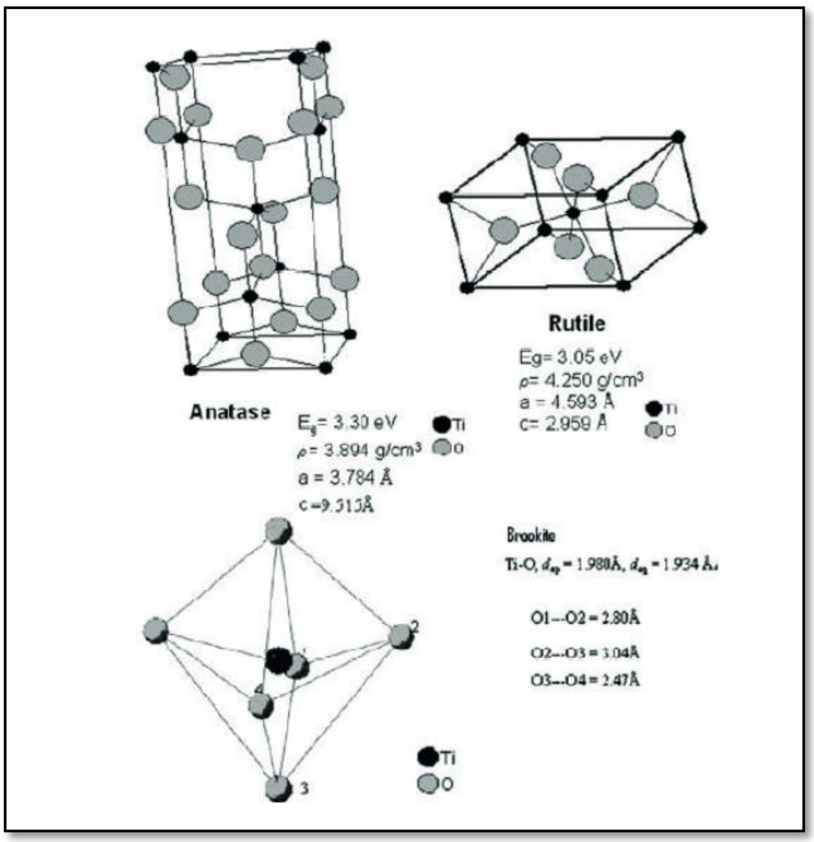


Figure 1. Two Crystallographic forms of Titanium Dioxide (Byranvand *et al.*, 2013)

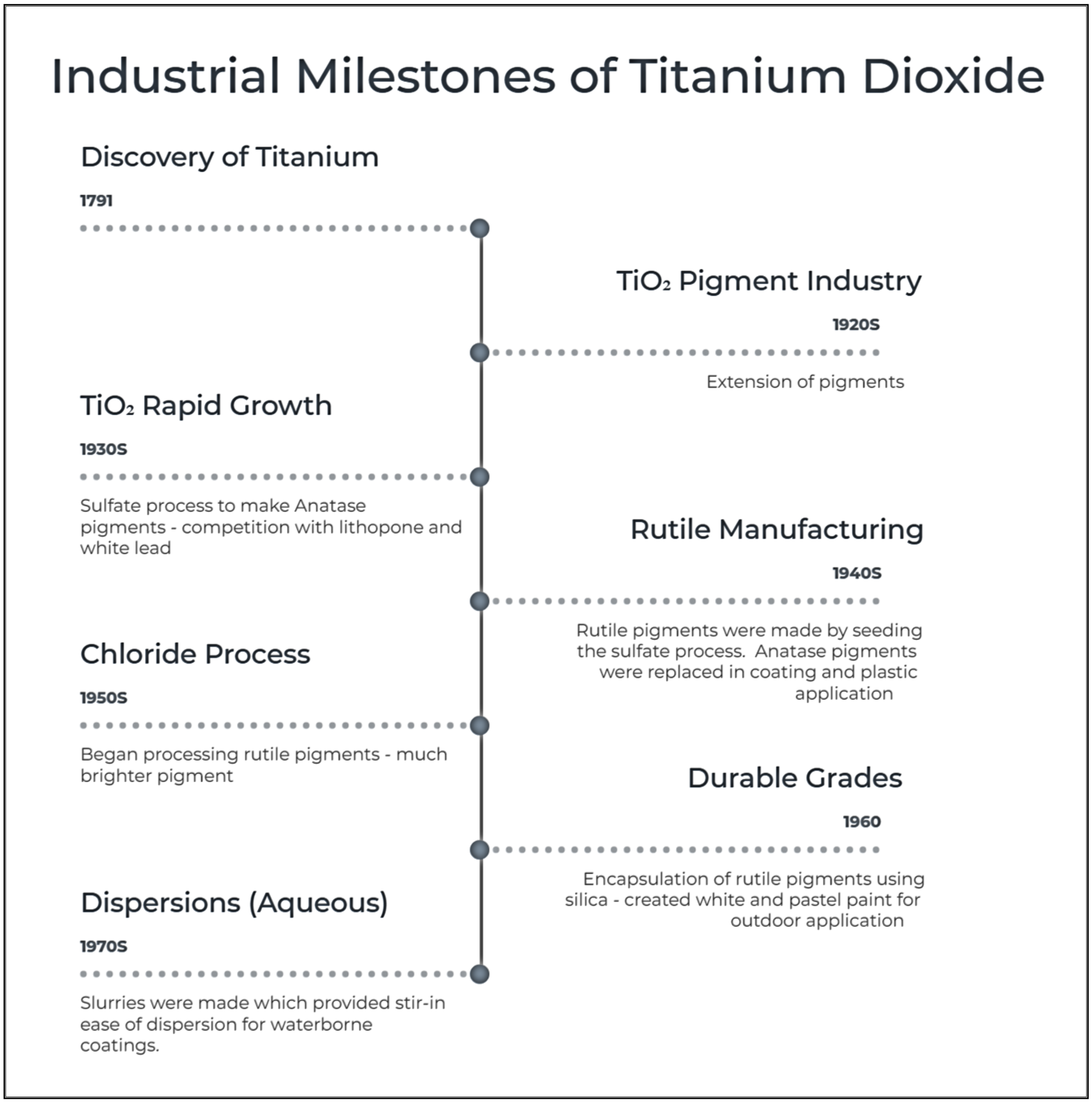


Figure 2. Timeline of Titanium Dioxide adapted from (Braun, Baidins and Marganski, 1992). Timeline created with Adobe Express.

1.2. Titanium Dioxide as a Food Additive (E171)

Food Additives are substances that are added to food for a specific purpose, they can be as an aid to processing, manufacturing, or any technological purpose such as preparation, processing, manufacturing aid, packaging, transportation, and even storage and these are then found in the ingredient declaration of a finished product. (European Parliament and the Council of the European Union 2008) (Ahmad Ruslan *et al.*, 2021). In the EU, It is necessary to label any food additive with "E number" as E171, apart from being an additive, it can also be used as a processing aid such as an anti-caking agents in the process of food production, in this case, any food additive used in this way is not needed to be labelled (Al-Mazeedi, Regenstein and Riaz, 2013). In the EU, all food additives are regulated by Regulation (EC) No. 1333/2008 with only specific list that may be used. Titanium Dioxide (TiO_2) was listed in the Appendix I, Class II (food colours without maximum quantity limits) which can be applied *quantum satis* ("as much as necessary, as little as possible") to most of the food, with no accepted daily intake (ADI) and recommended daily dose (RDI). . There has been a specification established by Regulation (EU) No. 231/2012, The European Commission stated that Titanium Dioxide may only consist of pure anatase and/or rutile for, it can be coated by aluminium oxide (Al_2SO_3) and/or silicon dioxide (SiO_2) with maximum limit of 2% (*Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council Text with EEA relevance*, 2012). In the USA, TiO_2 has been approved as a food additive in 1966 by Food and Drug Administration (FDA) with a limit of 1% in the food's weight (Jovanović, 2015). The most common products that uses E171 are candies, chewing gums, coffee creamers, toothpaste, nutritional supplements and other pharmaceuticals. The anatase crystalline form is primarily used as food additives and therefore exposure to this type is predominant among consumers. (Weir *et al.*, 2012; Chen *et al.*, 2013; Yang *et al.*, 2014; Dudefoi *et al.*, 2018). The group that experiences that highest level of exposure are children (Shi *et al.*, 2013). Its usage has risen over the later part of the 20th century, however, it has been seen to be declining due to concerns about its safety (Skocaj *et al.*, 2011).

Regulation No. 257/2010 of the European Union requires all food additives that were approved before January 2009 to undergo a safety re-evaluation. In accordance with this regulation, EFSA conducted a safety assessment of E 171 (Titanium Dioxide) in June 2016. Based on the assessment, TiO2 is harmless when ingested in terms of genotoxicity, and it does not cause cancer (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2016). However, there is a lack of conclusive data to determine whether it has any negative impact on the reproductive system. To establish final conclusions, either a 90-day study or a multi-generation or extended one generation reproductive toxicity study (EOGRTS; OECD test guideline 433) is required. As a result, no Accepted Daily Intake (ADI) value could be determined. Nevertheless, the EFSA determined that the Margin of Safety (MOS) was over 100, based on the estimated exposure of consumers and the established no-observed-adverse-effect level (NOAEL) value of 2250 mg/kg body weight/day, indicating that the use of TiO2 as a food additive is safe.

1.2.1. Nanotechnology

Since the last century, Nanotechnology has been in a well know field of research. It was first presented by a Nobel laureate, Richard P. Feynman, during his famous lecture in 1959 called "There's Plenty of Room at the Bottom'' (Feynman, 1992). Nanoparticle (NP) is defined as a class of materials which are in particulate substances that have a dimension of at least less than 100nm (Laurent *et al.*, 2008). The term "nanotechnology" was only recognized in the late 1980s during the applications in the industry has emerged. Due to concerns on health, risk of safety and environmental impact, the European Union have devised a regulatory framework as a protection from exploitation of the industry. (Justo-Hanani and Dayan, 2015). *The main objective is to have an environment that is favourable for its development* (Meisterernst, Daniel and Thron, 2006)

It was in 2004 that the European Commission have proposed an overall European Strategy for nanotechnology, which aligned in accordance to the Lisbon strategy which was to create an economy that is highly knowledge based and competitive. During this time period, there were not a distinct approach to regulatory, whereby nanomaterials were covered by regulations that have already existed and therefore became a 'soft law' with a code of conduct for responsible nanoscience and nanotechnology. It was not until October 2011 when the European Union have articulated and defined nanomaterials in as any material made up of particles with at least one dimension between 1 and 100nm in size that are either natural, manufactured or incidental, either unbound or aggregated with at least 50% of the particles need to fit this criteria. (Winkler *et al.*, 2018) (*Commission Recommendation of 18 October 2011 on the definition of nanomaterial Text with EEA relevance*, 2011)

During this particular period, the priority was to identify potential risks associated with chemical substances. Regulation (EU) No. 1907/2006, known as the Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulation, was established on December 18, 2006, in Europe. This regulation created the European Chemical Agency (ECHA), which manages the technical, scientific, and administrative aspects of REACH. Long term inhalation studies of rats exposed to high concentrations of TiO2 developed lung tumors (Lee, Trochimowicz and Reinhardt, 1985). As a result, the International Agency for Research on Cancer (IARC) (created in 1965) classified TiO2 as "possibly carcinogenic to humans" (category B2) at the pulmonary level. This classification raises doubts about the safety of other TiO2 grades, particularly those used in food and ingested by humans. Between 2008 and 2011, amendments were made to food regulations, requiring specific authorization for nano-foodstuffs and additives before they enter the market. In the European Union, food additives depend on Regulation (EC) No. 1331/2008 (for authorization procedures) and No. 1333/2008 (for rules on food colors) (*Regulation (EC) No 1331/2008 of the European Parliament and of the Council of 16 December 2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings (Text with EEA relevance)*, 2008). Policy No. 1169/2011 regarding the provision of food information to consumers was introduced in 2011. This policy requires all ingredients present in the form of engineered nanomaterials to be indicated in the ingredient list, followed by the word "nano" (in brackets) (*Commission Recommendation of 18 October 2011 on the definition of nanomaterial Text with EEA relevance*, 2011). The identification of nanomaterials for INCO is stricter than the European Union's definition of nanomaterials (2011/696/EU) because it doesn't have a threshold. Manufacturers face significant uncertainty because, according to INCO, any nanometric form present in the food chain must be indicated, whereas, according to the European definition, it is not considered a concern if there are less than 50% nanoparticles (Boutillier, Fourmentin and Laperche, 2020).

There are different classifications of NPs depending on their shape, properties or sizes. These include fullerenes, metal NPs, ceramic NPs and polymeric NPs. Due to nanoscale size and high surface area, there are unique physicochemical properties that differentiate NPs as opposed to fine particles (FPs) (Khan, Saeed and Khan, 2019).

TiO_2 has been seen to be one of the top five nanoparticles (NPs) that are used in consumer products (Shukla *et al.*, 2011). They are highly favourable in terms of price, high photocatalytic activity and uses not only in food but also in paints, textiles, paper, plastics, cosmetics, furniture, etc. (Rashid, Forte Tavčer and Tomšič, 2021).

Due to this extensive applications of TiO_2 NPs, there has been a significant concern on its health implication due to human exposure that may occur during manufacturing via inhalation and use via ingestion.

1.2.2. (Toxicokinetics)Ingestion of Titanium Dioxide

There has been a repeated question on the safety and risk of fgTiO_2 when ingested by human consumers. It was estimated that in the US, the intake of TiO_2 in adults were at 0.2-0.7mg TiO_2 per kg, body weight per day (mg/kg b.w./day) and children below the age of 10 had 1-2mg/kg b.w./day and with approximately 0.2-0.7mg/kg b.w./day for other consumer groups. In the UK, there is an estimated average of 2-3mg TiO_2/kg b.w/day amongst children under the age of 10 and 1mg/kg b.w/day for the other groups of consumers (Weir *et al.*, 2012). In Europe, It was estimated the consumption to be 5-9mg per person per day and even up to 34.9mg/kg per day amongst children (EFSA, 2019). It can be observed that, children are the highest consumers of TiO_2 with more than 4 times per day compared to adults (Weir *et al.*, 2012).

The National Institute for Public Health and the Environment (RIVM) in the Netherlands has assessed the levels of exposure based on industry data. Their findings indicate that children have an estimated exposure of 1.4 mg/kg body weight/day, while individuals aged over 70 have an exposure of 0.5 mg/kg body weight/day (C. Sprong et al., 2015).
Additionally, the European Food Safety Authority (EFSA) has conducted its own evaluation of maximum exposure levels for various age groups. According to the EFSA's estimates, children (infants to 9-year-olds) have an average exposure level ranging from 0.4 to 10.4 mg/kg body weight per day. Meanwhile, adults aged 18 to 64 years have an estimated exposure level ranging from 0.6 to 6.8 mg/kg body weight/day, and individuals aged 65 and above have an estimated exposure level ranging from 0.4 to 4.5 mg/kg body weight/day (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2016).

One of the first studies regarding the presence of the TiO_2 in small intestine after ingestion was in 1987. Macrophage pigments were identified specifically in Peyer's patch, which is located at the base of ileal lymphoid follicles amongst 42 patients with age as young as 2 days old to 70 years old whom were suffering from inflammatory bowel diseases (IBD) or other concerning inflammatory gut diseases. Using microscopy, Shepherd et al. found that patients who are older had more loading of macrophage with these black granular pigments. (Shepherd *et al.*, 1987). This hypothesis was supported when Hummel et al. did a further study on 151 children; 62 who had Crohn's disease (CD); 26 with ulcerative colitis; 63 who were controls that did not suffer from IBD. Biopsy results showed that there were black pigments deposit in 63 children which were found in Peyer's patches located in the terminal ileum. There was a positive correlation between the age of the children and the amount of deposited pigments found, however it also showed that patients who had CD had less compared to those with ulcerative colitis and those with non-IBD (Hummel *et al.*, 2014).

In a study conducted by Powell et al. 15 people in the UK with IBD and 5 people with colonic carcinoma showed particles of TiO_2 in the form of anatase with a particle size of 100-220nm in high concentrations in macrophages from gut-associated lymphoid tissue (GALT) macrophage using x-ray microanalysis (XRMA) and electron energy loss spectroscopy (EELS) (Powell *et al.*, 1996). Further studies on looking at whether a microparticle like TiO_2 would alter the responsiveness of intestinal cells to lipopolysaccharide (LPS). Larger sample size with a total of 85 subjects; 28 of which are ulcerative colitis patients; 21 who have Crohn's disease; 36 healthy participants as controls. Using bioassay and ELISA techniques, quantification of levels of interleukin 1 (IL-1) was determined and it showed that there was a significant increase when it comes to conjugate of LPS and TiO_2 up to 30-60 folds in comparison with controls. This study has conveyed that TiO_2 is not completely inert, especially with patients suffering from IBD as abnormal activity in the permeability of intestines (Powell *et al.*, 2000a). From these studies, it can be seen that ingestion of TiO_2 amongst those who suffer from IBD have a significant impact in the GALT.

Pele et al. conducted a study to investigate the presence of TiO2 in the bloodstream and found that it was detectable via reflectance microscopy and ICP-MS two hours after administering 100mg anatase fgTiO_2 gelatin capsules. The maximum concentration was observed after 6 and 24 hours (Pele *et al.*, 2015). This study was repeated on six volunteers using similar capsules. Conversely, Jones et al. reported that oral exposure to 5mg/kg b.w. of mixed micro and nano TiO_2 particles in water resulted in insignificant absorption (Jones *et al.*, 2015). In another study, Ruiz et al. found detectable levels of blood titanium in human patients, with higher levels observed in individuals with active ulcerative colitis (UC) than controls, UC remission patients, and Crohn's disease patients, regardless of whether their disease was active or inactive (Jones *et al.*, 2015). Heringa et al. detected elemental Ti in liver and spleen tissues obtained post-mortem from humans and hypothesized that the digestive system is the entry point for TiO_2. They also found TiO_2 particulates in intestinal and other tissues (Heringa *et al.*, 2018). Collectively, these studies demonstrate that fgTiO_2 can enter systemic circulation and accumulate in the GALT over time, and may worsen pre-existing inflammatory conditions. However, the consequences of fgTiO_2 accumulation in the body remain unclear.

Jovanovic (2015) conducted a review of 16 studies conducted between 1994 and 2014, which explored the toxic effects of TiO2 on mice and rats. The studies used primary particle diameters of TiO2 ranging from 5 to 475 nm, but it is unclear whether food-grade TiO2 was used. All studies, except one, demonstrated toxic effects in the animals, such as liver or kidney damage, inflammatory reactions, and changes in the spleen and heart. Most studies also observed bioaccumulation of TiO2 in the liver and spleen. According to the author, the review provides convincing evidence that TiO2 can be absorbed through the intestinal tract of mammals and can bioaccumulate in the tissues of mammals and other vertebrates. The spleen, liver, and kidneys were the most affected organs, and the severity of the histopathological and physiological changes varied depending on the TiO2 dose. The author also noted that TiO2 was only eliminated to a limited extent, and most studies used very high amounts of TiO2, which exceed the estimated intake levels for humans. The author criticized the fact that studies are often conducted without precise particle characterization (Jovanovic, 2015) (Jovanović, 2015).

According to Winkler et al. (2018), the safety of food additive E 171, or TiO2, remains uncertain due to data gaps in the available literature on its toxicokinetics and toxicology up until 2017. Long-term oral exposure to TiO_2 may pose health risks, with negative effects on the liver being a particular concern. It is recommended that the intake of TiO_2 through food be limited to less than 0.4 mg/kg body weight per day (Winkler *et al.*, 2018).

Schober et al. (2017) conducted a study on the toxicokinetics of titanium dioxide. The research involved five subjects who received a single oral dose of 45 mg of either nano- or microscale TiO_2 dispersed in demineralised water. The study did not clarify if the TiO_2 used was food-grade. Blood analyses indicated that nanoscale TiO_2 (8 nm particle diameter) and microscale (190 nm particle diameter) were equally poorly absorbed into the bloodstream through the intestine. During the observation period, blood concentrations mostly fluctuated within the range associated with diet-related fluctuation. There was no significant increase in the amount of titanium found in the urine of the subjects. The authors concluded that orally administered TiO_2 in all grain sizes is mainly excreted in the faeces (Schober *et al.*, 2017).

In 2017, Bettini et al. conducted a study on rats to investigate the impact of E 171, which was orally administered to test animals for seven days or via drinking water for 100 days. The E 171 used in the study had a nanoparticle proportion of 44.7%, and the rats had previously been injected with a tumour-promoting chemical substance. The study found that E 171 negatively affected the immune system, caused changes in the intestinal mucosa, and elevated certain inflammatory parameters. Moreover, the study showed that E 171 could trigger changes in the intestine that might indicate precancerous stages. Following this study, the French government banned the use of E 171 for one year starting from 01.01.2020 (Bettini *et al.*, 2017).

However, in a study by Blevins et al. in 2019, rats were fed with E 171 instead of it being administered via drinking water or gavage. The study found no effects on the immune system or tissue morphology in the animals, even in the group that received the highest dose. The authors suggest that the food matrix in which E 171 is embedded could be a crucial factor for toxicity (Blevins *et al.*, 2019). A study by Zhang et al. also supports this idea, as it revealed that a selected food simulant reduced the cell toxicity of TiO_2 nanoparticles in vitro by more than 5-fold (Zhang *et al.*, 2019).

A study conducted in Australia in 2019 investigated the effect of E 171 on the intestinal flora of mice. The animals were given the food additive in doses ranging from 2 to 50 mg/kg body weight per day in their drinking water for a period of 3-4 weeks. The study found that while E 171 only had a slight effect on the composition of the intestinal flora, it significantly impaired the immune system's ability to stabilize and regulate the intestinal flora, leading to inflammation. The authors of the study concluded that prolonged exposure to E 171 could potentially increase the risk of conditions such as inflammatory bowel disease and colon cancer (Pinget *et al.*, 2019).

1.2.3. Inhalation of Titanium Dioxide

The primary pathway by which nanoparticles enter the body is through inhalation (Yang, Peters and Williams, 2008; Praphawatvet, Peters and Williams, 2020). Once inhaled these NPs can undergo through different pathways such as in the alveoli, capillaries, lungs and transported to the heart, liver and nervous systems. The anatase form is more toxic compared to the rutile due to its finer particles (Christensen *et al.*, 2011).

The occurrence of inhalation can be observed mostly in occupational settings such as during the manufacturing of TiO_2 powder or products which contain TiO_2 (Hext, Tomenson and Thompson, 2005). It has been seen that the areas of milling, packing and cleaning have the highest exposure. One of the earliest studies in Japan, a 53-year-old male who had been involved in packing TiO2 for approximately 13 years and had a 40-year history of smoking was reported to have papillary adenocarcinoma and TiO2-associated pneumoconiosis in his lung (Yamadori, Ohsumi and Taguchi, 1986). A study conducted by Fryzek e al. on factory workers and it has been discovered that the highest exposure to TiO_2 were the people who are in the packing, addback and micronizing areas, with exposure levels 6.2±9.4 mg/m^3, compared to the ore handlers with a low level of 1.1±1.1mg/m^3 (Fryzek *et al.*, 2003). Similar study by Boffetta et al. had looked at the six European factories and its exposure to TiO_2 dust, it has resulted to have a variation average between 0.1 to 1.0 mg/m^3 annually. However when it came to different individual job categories, it was higher at 5mg/m^3, which indicated that there is a variation of exposure depending on the area of production and it exceeded limit of time weighted average of 10 h TWA by National Institute for Occupational Safety and Health (NIOSH) (Boffetta *et al.*, 2004; 'Current intelligence bulletin 63: occupational exposure to titanium dioxide.', 2020).

1.3. Regulations and ban of Titanium Dioxide in the EU

The European Food Safety Authority (EFSA) issued a recommendation in 2018 on the potential risk of nanoscience and nanotechnologies on food and feed safety. This prompted to generate of information on the toxicokinetic properties of engineered nanomaterial (ENM) and the conduction of risk assessment must be undertaken as per case-to-case basis due differences in toxicity (EFSA, 2018) (Committee *et al.*, 2018).

Due to the doubt of safety that surrounded the use of Titanium Dioxide, the French Government decided to follow the principle of precautionary with the advice opinion of the "Agence Nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail" (ANSES) to have a ban of its usage at the start of 1st January 2020 and this was prolonged for another year (Le Maire and De Rugy, 2020). It has been decided that the reason for this ban were the uncertainties regarding the health effect on consumers, particularly the titanium dioxide nanoparticle.

Starting from the 2010s, food-grade TiO2 has come under increased scrutiny due to its potential health risks, as evidenced by numerous scientific studies (Bettini et al. 2017; Houdeau et al. 2018; Carriere et al. 2020; Guillard et al. 2020; Bischoff et al. 2021). In 2012, it was found that food-grade TiO2 samples contained 36% of nanoparticles (Weir et al. 2012). In 2016, the European Food Safety Authority (EFSA) reapproved the use of TiO2 in food but did not determine its admissible daily intake due to the insufficiency of research data (EFSA 2016). However, the questioning of the safety of food-grade TiO2 intensified since 2017, driven by new scientific studies, especially in France. A study conducted by INRAE on rats in 2017 showed the carcinogenic effects of TiO2 on the digestive system, prompting the French government to request ANSES to advise on the conclusions of the study (Bettini et al., 2017). This study displayed the development at first stages of colorectal carcinogenesis for 40% of rats exposed to TiO2 for 100 days at low dose. ANSES acknowledged the need for further studies to fully understand the risks of food-grade TiO2. Following this, France requested the suspension of the marketing and use of TiO2 as a food additive, and the French Egalim Law suspended its use as a food additive in France. France also requested the suspension of marketing and use of TiO2 in Europe and suspend imports of the product.

In 2019, ANSES conducted a review of the literature and highlighted the lack of scientific data to resolve the uncertainty regarding the safety of food-grade TiO2. The EFSA confirmed that TiO2 was not carcinogenic after oral administration but recommended additional investigations to reduce uncertainty. The recent decision to ban the use of TiO2 in food at the European level is largely based on the French decision taken in 2019, but also on various publications demonstrating the risks of TiO2, particularly for pregnant women. The regulation of TiO2 as a food additive has evolved in the context of the regulation of nanotechnology, and the case of food-grade TiO2 demonstrates the evolving nature of chemical product regulation under the influence of various stakeholders, including academics and non-governmental organizations.

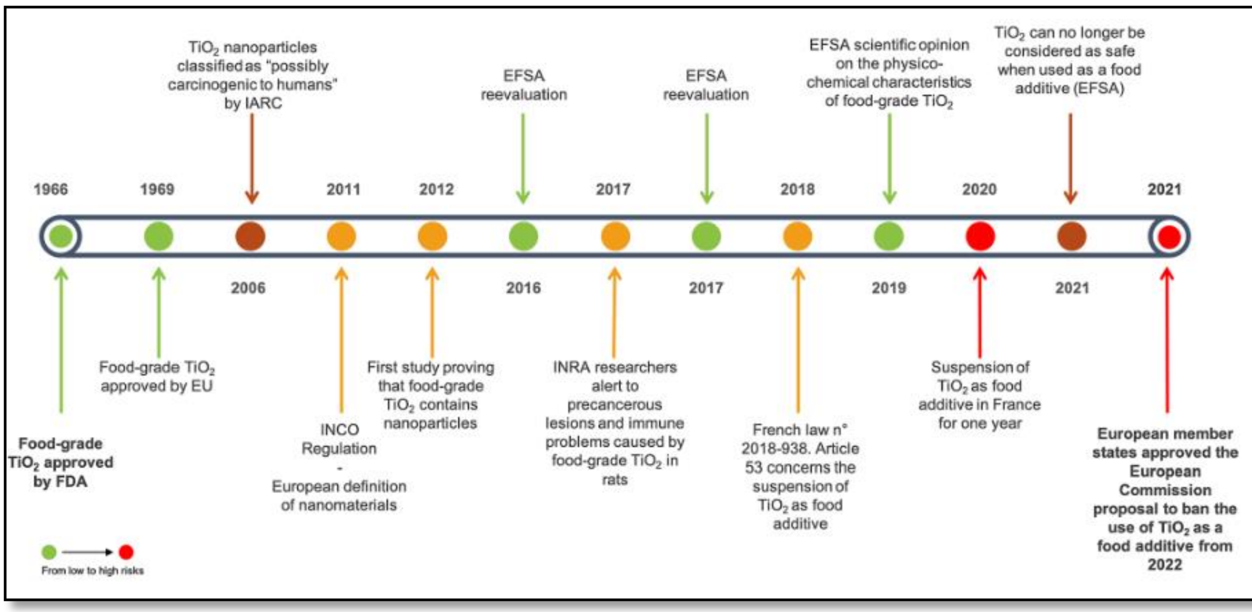


Figure 3. History of the food-grade Titanium Dioxide (fgTiO_2) from Food and Drug Administration (FDA); International Agency for Research on Cancer (IARC); European Food Safety Authority (EFSA), INCO: (EC) n°1169/2011)

From then on, the European Food Safety Authority (EFSA) concluded that TiO_2 as a food additive is no longer considered safe on 6th May 2021 and the European Commission (EC) proposed its complete ban from 2022 onwards as agreed and approved by members of the state.
Commission Regulation (EU) No. 2022/2063 of to withdraw the authorization to use titanium dioxide in food products. As a result, titanium dioxide will no longer be authorized for use in foods or in food supplement products in the European Union as of August 7, 2022.

The Feed additive for all the animal species have also been involved in the ban of the titanium dioxide and must be withdrawn from the market by June 20, 2022 with the Commission Implementing Regulation (EU) 2021/2090 as of 25 November 2021.

Country	Banned from	Comment
European Union **FOOD**	August 7, 2022	Ban has been approved for food uses.
European Union **FEED**	June 20, 2022	Denial of authorization of titanium dioxide as a feed additive for all animal species.
Switzerland	September 15, 2022	Following the EU Ban for foods.
Gulf States (GCC)	21 October 2022	Following the EU Ban for foods.
Saudi Arabia	21 October 2022	Following the EU Ban for foods.
Yemen	25 September 2022	Following the EU Ban for foods.
Qatar	15 October 2022	Following the EU Ban for foods.
Israel	01 June 2023	Following the EU Ban for foods.
Turkey	15 November 2022	Proposed to update Turkish regulations to align with updates to EU. Recent information from the TiO_2 working group states Turkey is skeptical of a ban. However, no formal information as of yet.
Jordan	June 8, 2022 January 1, 2023	Per the Jordanian Chamber of Commerce. No Import of products with TiO_2. JFDA deadline on the complete ban.
Israel	October 31, 2022	WTO notification. Following the EU Ban for foods. No comments yet about pharma.

Table 1. Countries that have a ban on TiO_2 adapted from reputable governmental agencies

Countries Considering a ban

Country	Comment
Brazil	ANVISA currently evaluating, no position yet.
Argentina	ANMAT/INAL currently evaluating, no position yet.
Mercosur Countries	Regulators currently evaluating, no position yet.
Colombia	Regulators currently evaluating, no position yet.
Japan	MHLW currently evaluating, no position yet. TDMA study package sent 11 August 2022. They are neutral at this time and have no intention to take immediate action.
South Korea	MFDS currently evaluating, no position yet. Difficult to get feedback.
Russia	No plans to take action at this time, but it is expected to follow EU
Thailand	Neutral and awaiting JECFA

Table 2. Countries considering a ban

The above table contains relevant information with combination from online resources and reputable government bodies

Countries Skeptical of the ban

Country	Comment
United States	US FDA confirming that their position is that the available safety studies do not demonstrate safety concerns connected to the use of titanium dioxide as a color additive.
Canada	Health Canada published Report stating that TiO is Safe
Australia and New Zealand	In line with the outcomes of recent reviews of EFSA opinion, conducted in the United Kingdom (UK) and Canada, Food Standards Australia New Zealand (FSANZ) found no safety concerns
UK	UK will continue use of E171. Food Standards Agency conducts independent review of EFSA opinion and risk assessment. Timeline for risk assessment to conclude: Q1 / 2023
South Africa	SA will not take any actions at this time. Use will be reviewed if JECFA has re-evaluated its safety when new evidence is available

Table 3. Countries skeptical of the ban adapted from… reference all that's in the table

The United States Food and Drug Administration (FDA) has reaffirmed the safety use of titanium dioxide as a colour additive in foods and has communicated this to the Titanium Dioxide Manufacturers Association (TDMA) and confirmed that

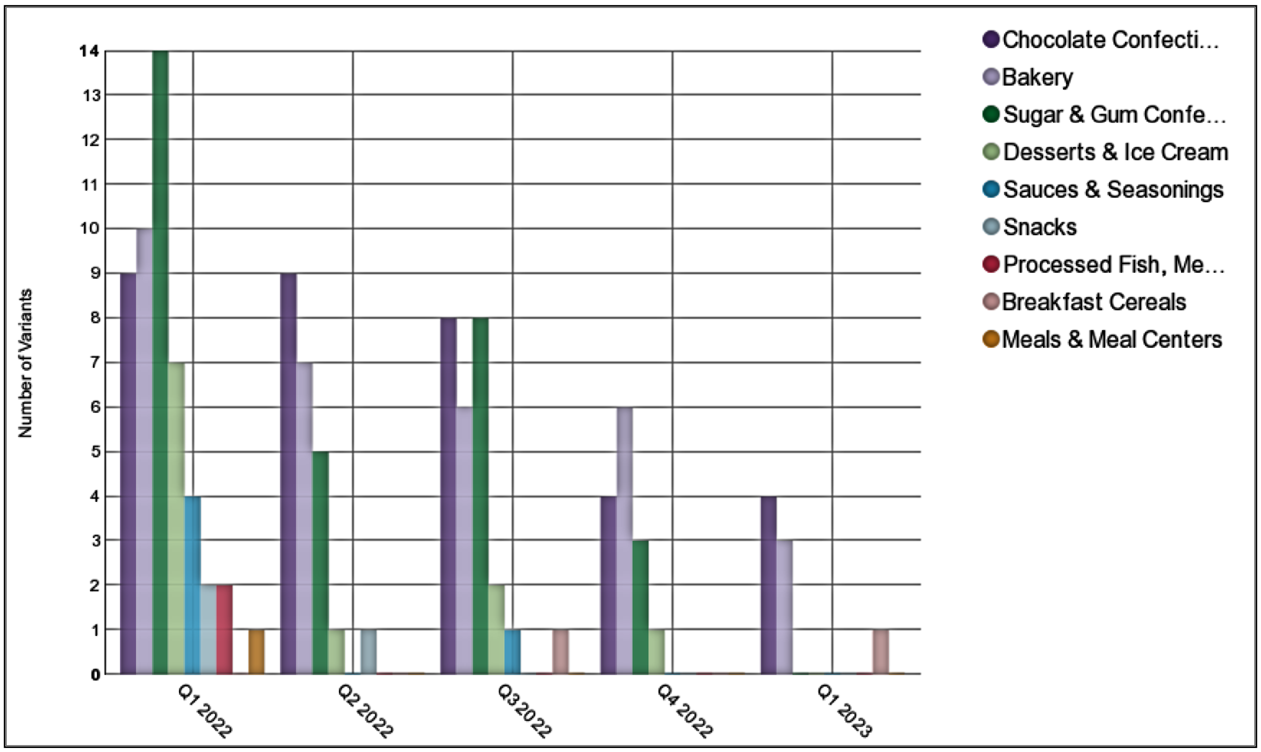
Similarly, Health Canada has published and issued a report completed by the food directorate regarding the safety of TiO_2 as a food additive. Within this, it was concluded that there was no evidence of any cancer related disease as well as adverse effects in studies with mice and rats being highly exposed to food-grade TiO_2. There were no evidence in adverse effects on development, reproduction, DNA, gastrointestinal, nervous systems and overall general health when rats were exposed. Based on this review, it was announced that there won't be a ban in Canada due to inconclusive scientific evidence on health in human. However, this may be revisited in the future following new studiew upon availability (Health Canada, 2022).

Classification Change of TiO2

Recent judgement by the Court of Justice of European Union (EUGH), repealing the decision of the EU Commission to classify Titanium Dioxide as a carcinogen by inhalation under the Classification, Labeling and Packaging of Chemicals (CLP) legislation, has been declared null and void.

1.4. Market Overview of Titanium Dioxide in Food Industries

Food Industries have declined their usage of Titanium Dioxide as a food additive from the beginning of 2022 to the first quarter of 2023. The biggest market is sugar and gum confectionery, followed by desserts and ice-cream with chocolate confectionery being the third biggest market.



Category	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Q1 2023	% change: Q3 2022 - Q4 2022	Total Sample
Chocolate Confectionery	**9**	**9**	**8**	**4**	**4**	**-50.0%**	**34**
Bakery	10	7	6	6	3	n/a	32
Sugar & Gum Confectionery	14	5	8	3	0	-62.5%	30
Desserts & Ice Cream	7	1	2	1	0	-50.0%	11
Sauces & Seasonings	4	0	1	0	0	-100.0%	5
Snacks	2	1	0	0	0	n/a	3
Processed Fish, Meat & Egg Products	2	0	0	0	0	n/a	2
Breakfast Cereals	0	0	1	0	1	-100.0%	2
Meals & Meal Centers	1	0	0	0	0	n/a	1
Total Sample	49	23	26	14	8	-46.15%	120

Figure 4. Food Category based on usage of Titanium Dioxide from Q1 2022- Q1 2023 (Mintel, 2023)

1.4.1. Confectionery

Confectionery food sector present the biggest value for Titanium Dioxide as a food additive, it is widely used in jellies, chews, lollipops, sugar coated candies, baked goods, powdered sugar toppings like icings and chewing gums.

A study conducted in the USA in 2012 which comprised of 89 different food products showed that the highest amount of E171 content (measured as titanium) is present in powdered doughnuts with 100mg per serving (Weir *et al.*, 2012).

Chewing gums with hard coated outer layer have had the highest titanium concentrations similarly to confectionery products with coated hard outer shells as well as coated peanut (Gressler *et al.*, 2020). In fact, it has been observed that chewing gum contains one of the highest concentration of TiO_2, with mean average weight per piece between 1416mg (±27mg) and 2240 mg (±86mg). (Weir *et al.*, 2012; Chen *et al.*, 2013; Ropers *et al.*, 2017; Dudefoi *et al.*, 2018).

A recent study in China by He et al. focused on the levels of exposure of TiO_2 in the dietary consumption of the Chinese population. An analysis of particle size and micro distribution was assessed in food products and it was found that the particle size of TiO_2 used as food additives was between 53.5 to 230.3 nm, with NPs accounted for 34.7% and chewing gums was between 56.8 to 267.7 nm with accounted NPs of 55.6%. (He *et al.*, 2022).

1.4.2. Dairy

There has been a need to use TiO_2 on dairy fat-free products to replace the creamy, fatty and white appearance.

Dairy products like mayonnaise, cheese, custard powder, coffee creamer, spray cream have been observed to only contain low concentrations of TiO_2 between 0.01mg to 1mg titanium per serving (Weir *et al.*, 2012).

A study in the Netherland by C. Sprong et al. in 2015 have found that baked good, desserts and sauces contain the highest content of E171 (C. Sprong et al., 2015)

1.4.3. Pet food

Titanium Dioxide has been used and found as feed additive in dog and cat food (Aldrich, 2019) With the similar function in human food, TiO_2 enhances the colour of white brilliance and opacifying properties to both dry and wet food. Two studies that Beynen (2021) had reviewed from Furr et al. (1976) with wet dog food (n=21) and cat food (n=4) and mean ranges of total titanium 166/0.2-1, 900 and 8/4-11mg Ti/kg of dietary dry matter (ddm) respectively and Fernandes et al. (2018) with dry puppy (n=32) and adult (n=63) dog foods with min/max titanium levels of <9/2,140 and <9/2,300mg Ti/kg ddm respectively. This has an overall total of N= 120 dry and wet pet foods and both procedure tests were conducted using instrumental neutron activation. Foecal studies were done with TiO_2 being used as a marker for estimation of produced faeces in digestibility test of both feline and canine.

It was determined the foecal recovery of titanium from dry dog food containing 0.3% titanium dioxide. For two distinct diet formulations, the probable absorption was 23% of intake, with recoveries ranging from 74 to 81% on average.

Similary, an experiment of TiO_2 with brought forth chicks as the sole wellspring of sustenance. The average faecal recovery ranged from 81 to 74%. On the off chance that the assortment of defecation in the three canine examinations was practically finished, It can be deducted that complete retention of titanium was roughly 16% of the admission, which would leave with a huge portion ingested. (Chippano and Carbajo, 2022)

1.5. Alternatives of Titanium Dioxide

There is a limited studies on the literature on the different alternatives to Titanium Dioxide, this could be due to the most recent ban in the European Union. The Food Industry continues to source a replacement for fgTiO_2.

1.5.1. Calcium carbonate (E170)

Calcium Carbonate ($CaCO_3$) occurs frequently in rocks in the form of minerals such as calcite and aragonite. It serves as a primary constituent of egg shells, gastropod shell, shellfish, skeleton and pearls. It is a prevalent ingredient/additive in food and pharmaceutical products. It is a good source of calcium and it has been used as a food additive (E170), colouring agent, acidity regulator, anti-caking agent, bulking agent (Belton, Hickman and Perry, 2019). A study in 2004 aiming at examining a whitening property and gel-forming ability of $CaCO_3$ along with two other compounds titanium dioxide (TiO_2) and soybean oil in a surimi (a mixture of bigeye snapper and mackerel). As expected, TiO_2 performed the best in whitening the surimi without any negative effect on the gel-forming ability, soybean reduced the gel-breaking force and caused deformation. Lastly, $CaCO_3$ did not produce any noticeable increase in whiteness and no improvement on the fore and deformation (Benjakul, Visessanguan and Kwalumtharn, 2004)

In contrast to this, a more recent study conducted in Tunisia in 2021 looked at the effects of whitening agents namely Calcium Carbonate ($CaCO_3$), Hydrogen Peroxide (H_2O_2) and Sodium Bicarbonate ($NaHCO_3$) in sardine surimi. Principal Component Analysis (PCA) was applied and results were shown that there is a significant enhancement of the whiteness of surimi when $CaCO_3$ and H_2O_2 were added as opposed to $NaHCO_3$ ($P < 0.05$). The PCA analysis bi-plot also demonstrated that 1.5% of $CaCO_3$ tended to produced surimi with improved whiteness, textural properties and water holding capacity (Zaghbib, Arafa and Mnasser, 2021).

1.5.2. Calcium Sulfate (E156)

Calcium sulphate ($CaSO_4$) is a white or white yellow, odourless powder or crystalline solid. It has a density of 2.96g/cm^3. (PubChem, 2023) An evidence from the literature on the whitening properties of $CaSO_4$ was derived from as study on using $CaSO_4$ dihydrate as a bleaching agent for crude soya bean vegetable oil. In order to make the soya bean oil edible and improve market value, it is necessary to remove its impurities, which includes gums, phosphatides, trace metals and free fatty acids. Therefore, it undergoes a bleaching process and for this study, $CaSO_4$ as different weight ratios relative to crude oil were prepared. The findings revealed that as the weight ration of the bleaching agent increased, there was a reduction in the red colour of crude soya bean oil. This effectively concluded that $CaSO_4$ can be used as way to bleach oil (Chakawa *et al.*, 2019).

1.5.3. Tricalcium phosphate (E341(iii))

Tricalcum phosphate $Ca_3(PO_4)_2$ (TCP) is one of the most important type of calcium phosphate in the food technology and biology (Enax *et al.*, 2022). It is odourless, tasteless, non-hygroscopic, soluble in acids with typical pH of 4 to 5 and at neutral pH it has a lower solubility compared to other calcium phosphate types i.e. hydrogen phosphates and dihydrogen phosphates (Dorozhkin and Epple, 2002). The solubility of calcium phosphates has a positive correlation to increase in temperature (Dorozhkin, 2009). It also has a tendency to neutralise acids without releasing gas in form of calcium carbonate or sodium carbonate. In the food industry, it is widely used as a white pigment that created opaqueness and turbidity in soymilk and other nutritional rinks as well as in preparation of fish. It is also a valuable texturiser of flour.

Food and Drug Administration (FDA) has recognised calcium phosphates as safe (GRAS), the World Health Organisation (WHO) in 1982 has also given approval to use calcium phosphate as food additive such as an acidity regulator, a treatment for flour, nutritional supplement source of phosphate and calcium, whitener, texturiser and thickening agent.

1.5.4. Tricalcium citrate (E333)

Tricalcium citrate is a white, odourless, crystalline powder that is freely soluble in diluted hydrochloric acid and slightly water soluble. It the most commonly used calcium salt of citric acid which is produced when the citric acid is completely neutralised with high purity of calcium from either calcium hydroxide or calcium carbonate. It has a high calcium content of 21% which makes it the most economic calcium salt. **(AG, no date)(Website).**

1.5.5. Starch

Starch based options from rice or corn sources are very common in creating an opaqueness in different types of application. This is by far the most common none E number formulation in the market that can be classified as ‘clean label’ solutions for whitening food products.

1.6. Food Industries – What are they doing?

1.6.1. Oterra (CHR Hansen)

Oterra has been in the market since their very first launched in 1876.It was founded by Chr. Hansen in Denmark and started their colour pigment, Annatto for cheese and butter.

The company is highly focused on natural food colours. It has 750+ employees across 40 nationalities with 27 countries with manufacturing facilities, labs and offices, 80+ agronomy, pigments and application scientist. They have more than 5000 customers within 112 countries (Oterra, 2023).

Oterra's Story

1800s

1874 – Chr. Hansen is founded in Denmark

1876 – Annatto color for cheese and butter launches at World Exhibition in Philadelphia, USA

1900–1949

1929 – Factory with color R&D facility opens in Milwaukee, Wisconsin USA

1939 – Natural color range expands to include red beet, grape skin and paprika

1941 – Dandelion Brand Butter Color trademarked

1950–1999

1964 – Factory for carmine production opens in Quilmes, Argentina

1979 – Listed on Copenhagen stock exchange

1988 – Acquires Spanish factory specializing in paprika and natural beta-carotene called Extract Oil

1988 – Establishes annatto plantation in Belém, Brazil

1991 – R&D moves from Milwaukee, USA to Copenhagen, Denmark

1995 – Enters joint venture in India to manufacture natural colors from turmeric and paprika called AKAY
- Acquires a French company specializing in anthocyanins and grape polyphenols called Sefcal
- Acquires a Spanish company specializing in carmine called Navarra

1996 – Launches CapColors® for brighter, more stable and more cost-effective colors

1999 – Acquires what is now our flagship factory for minimally processed colors in Italy
-Acquires Quest Color business with factory in Ireland

2000 – today

2003 – Acquires carmine production factory in Lima, Peru

2005 – Acquired by French private equity fund PAI

2010 – Listed on Copenhagen stock exchange for the second time

2011 – Launches I-Colors® for powdered applications and FruitMax® minimally processed range

2014 – Opens Global Expertise Center in Shanghai, China to address increasing consumer concerns about food quality

2019 – Launches Hansen sweet potato™ – wins first of three innovation awards

2021 – Acquired by Swedish private equity firm EQT and changes name to Oterra™
- Acquires Secna Group in Spain and Italy with expertise in organic caramel and anthocyanins
- Acquires Diana Food's natural food coloring business in France with expertise in organic red beet and orange carrot

Figure 4. The image above illustrated the timeline history of Oterra (Oterra, 2023)

1.6.1.1. Whitening Solutions - CAPCOLORS®

(CNS MEDIA, 2009)CAPCOLORS® White 100 WSS-P has been launched by Oterra, It is a calcium based product that is made using encapsulation technology with modified starch (Rasmussen, Koehler and Anderson, 2014), which makes it resistant to manufacturing process such as pH, light, oxidation and heat. The main application is targeted to chewing gums and chocolate dragées (CNS MEDIA, 2009).

1.6.2. Döhler

Döhler is one of the biggest natural ingredients, ingredient systems and integrated solutions Food Company with its headquarters in Darmstadt, Germany. It has more than 25,000 applications in food market with more than 8,500 employees (which include 1000 Scientist in R&D and technology) which operates in 45 manufacturing sites and 75 offices with customers in more than 160 countries. The product portfolio of Döhler ranges from all natural colours, flavours and health ingredients. It also has a range of plant based ingredients. (Döhler, 2023b). It had started as a spice mill almost 180 years ago, established in 1838 in Erfurt, Germany.

1.6.2.1. Whitening Solution - White Diamond™

Döhler has developed White Diamond™ which is an alternative for TiO_2, free from nanoparticles, acid stable, creates an opacity and whiteness in different food products such as creams in bakery, powder in beverages, hard boiled candy and pan coating in confectionery. (Cox, 2022; Innovations Admin, 2022) It has two type of products with a variation of particle size of 1 and 4µm (Döhler, 2023a)

1.6.3. Sensient Food Colors

Sensient Technologies began as Meadow Spring distillery in 1882 where it made gin and whiskey. Due to the probihition in 1919, it had to diversify and have started to create a business in marketing yeast with the packaging brand called Red Star Yeast.

There has been further expansion and operational growth during the 1960s that the company was renamed to Universal Foods that sold commodity products like frozen potatoes, cheese and yeast.

Like many companies, the need for acquisition and expansion has become a business strategy and in 2000, the company has changed its name to Sensient Technologies with its headquarter in Milwaukee, Winsconsin. Today, It is a globally recognised company with customer over more than 150 nations and more than 3800 employees worldwide. The company is broken down into segments including Food and Bevergae Flavors, Food and Beverage Colors, Cosmetic Ingredients and Pharmaceutical Excipients.

1.6.3.1. Whitening Solutions – Avalanche™

Sensient Food Colors first launched the portfolio of Avalanche™ - the new white in 2013. . The range of products have been develop specific to it different applications such as confectionery, instant drinks, pet food and sauces (Wyers and Green, 2017). Sensient has 4 different portfolio platforms namely MB, Fusion Xtra, Nebula and Ultra.

Below is the breakdown of the products as per the Sensient product sheet (Sensient Food Colors, 2023)

AVALANCHE™ MB SOLUTIONS

- Whiteness/opacity in low to high-water activity applications
- Superior heat and extrusion stability
- Improved acid stability
- Solutions without pH impact available
- Reduced foaming compared to standard calcium carbonate
- Microfine versions available for better mouthfeel and overall taste profile
- Simple ingredient alternative to TiO_2
- Kosher and Halal suitable

AVALANCHE FUSION™

- Simple ingredient alternative to TiO_2
- Brilliant white shades
- Good heat, light, and pH stability
- Kosher and Halal

AVALANCHE™ XTRA

- Brighter, brilliant white shades
- Increased performance and efficiency at lower usage rates
- Enhanced stability without impact to flavor, texture, and viscosity
- Topical coating and frosting systems available
- Label-friendly and preservative-free
- Kosher and Halal

AVALANCHE™ ULTRA

- Opacity in mid-to-high water activity applications
- Maintains cloud and opacity in prepared dry mixes
- Sustained viscosity under retort processing
- Remains suspended after hydration for improved opacity
- Good heat, light, and pH stability
- Label-Friendly
- Kosher and Halal

(Sensient Food Colors, 2023)

1.6.4. ADM

ADM (Archer Daniels Midland Company) was founded in 1902 in the USA by George Archer and John Daniels, both of them have begun a linseed crushing business in Minneapolis, Minnesota. The company has operation of more than 270 manufacturing plants and 420 crop procurement facilities. There has been a big transformation in ADM with the company's numerous acquisitions and diversification in different categories of food, beverages, nutraceutical, industrial and animal feed (ADM, 2023).

Figure 5 The image above illustrated the timeline history of ADM (ADM, 2023)

1.6.4.1. Whitening Solutions – Pearl Edge™

A new line from ADM was launched called Pearl Edge™ proprietary portfolio that is derived from natural resources which includes native corn starch. It offers to create a uniform, stable and brilliant whitening properties to food and beverages. It is tailored for confectionery, beverages including drink mixes, bakery, icings, fillings as well as sugar free offerings. It can also be applied to dairy and meat alternative and also with pet food. This is the company's offering to a clean and safe solution as an alternative to TiO_2 (ADM, 2023).

Pearl Edge™ Silk, Pearl Edge™ Satin, Pearl Edge™ Shine and Pearl Edge™ Shine+ are products in powder format that are said to be game-changers for its white and smooth appearance and texture in products especially in panned coated confectionery and compressed tables. As for sugar free solution applications, PearlEdge™ Star-Lite is recommended.

PearlEdge™ Splash and PearlEdge™ Splash+ are products that elevated the opacity and cloudiness of beverages with no ringing effects, precipitation, sedimentation or even staining in both alcoholic and non-alcoholic beverages. This product is formulated using their very own emulsion technology (ADM, 2023).

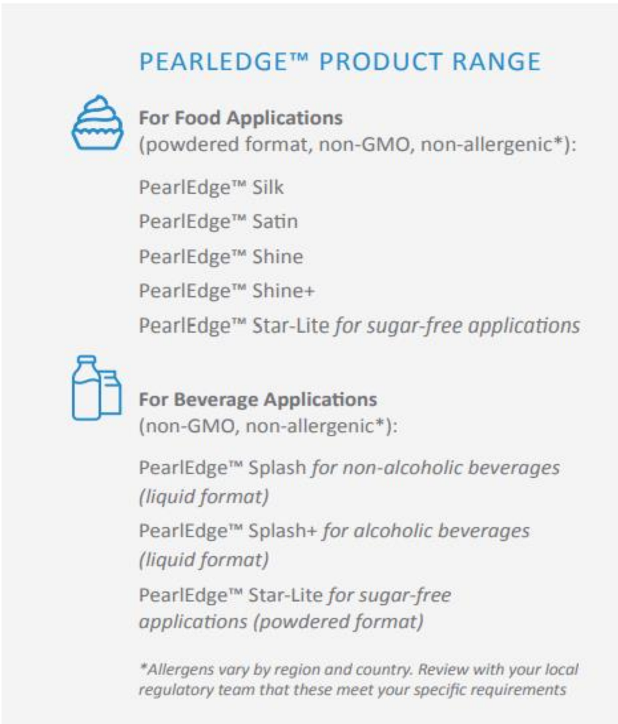


Figure 6. The image is from the ADM website on the PearlEdge™ Product Brochure (ADM, 2023)

1.6.5. ROHA

ROHA have started in its small office in Maharashtra, India primarily manufactured synthetic colours in 1972 for industrial applications. It has since evolved into one of the leading multinational company manufacturing natural food colours, ingredients, cosmetic pigments, pharmaceutical, dried ingredients along with industrial colours and dyes.

It is a part of JJT Group and its headquarters have stayed in India with 22 operating countries across departments in manufacturing, logistics and regulatory (Roha, 2023).

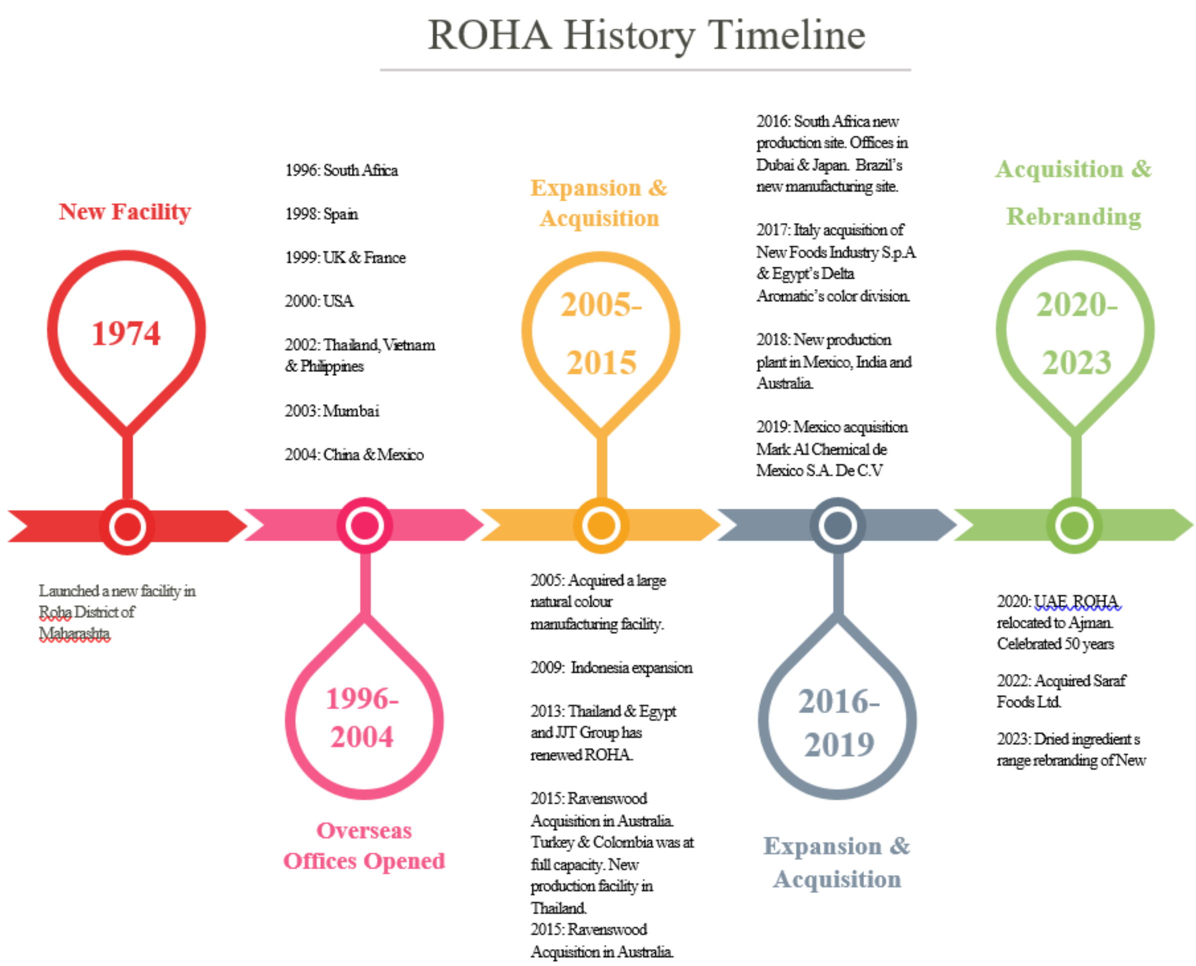


Figure 7. Image adapted from ROHA History Timeline (Roha, 2023)

1.6.5.1. Whitening Solutions –NATRACOL NIVEOUS

In order to create a match for replacing TiO_2, ROHA has developed the Niveous range for confectionery products like pan coated sweet, jellies, and gummies as well as beverages. There are blends of calcium carbonate and/or starches which mimicks the appearance of natural whiteness and mimicks the opacity of titanium dioxide (ROHA, 2023).

NIVEOUS Product Portfolio

- **Confectionery -** Natracol Niveous Pearl | Natracol Niveous Ivory | Futurals Pro Niveous Rime | Futurals Pro Niveous Moon | Futurals Pro Niveous Lily
- **Beverages** - Natracol Niveous Aqua | Futurals Pro Niveous Aqua

Below is the breakdown of the Roha portfolio as per the product sheet (Roha, 2023)
Natracol Niveous Pearl
Clouding effect in gummies
Starches (Rice, Tapioca) Starches (Rice, Tapioca), Color (Calcium Carbonate E170), Sucrose Ester E473 (As Carrier for Food Additive

Natracol Niveous Ivory Panned Candies Gummies Jellies
Low cost Natural Alternative to TIO2 in Confectionary Applications.
Color (Calcium Carbonate E170)

FUTURALS PRO NIVEOUS RIME – Panned Candies
A Coloring Food Option That Provides a Great White Base For Panned Candies as well as a Clouding Effect In Gummy Applications. E-Number Free "Clean" Label Solution
Starches (Rice, Tapioca), Emulsifier (Sucrose Ester E473)

FUTURALS PRO NIVEOUS MOON Panned Candies
A Coloring Food Option Without Any Emulsifiers That Provides a Great White Base for Panned Candies as well as a Clouding Effect in Gummy Applications. E-Number Free "Clean" Label Solution
Starches (Rice, Tapioca)

FUTURALS PRO NIVEOUS LILY Panned Candies

A Coloring Food Option Without Any Emulsifiers That Provides a Great White Base for Panned Candies as well as a Clouding Effect in Gummy Applications. E-Number Free "Clean" Label Solution

Rice Starch

Beverages

NATRACOL NIVEOUS AQUA

A Sustainable Natural Clouding Agent with a Better Settling Rate Than TIO2 in Beverage Applications. A "Cleaner" Label Representation Vs TIO2

Color (Calcium Carbonate E170) Acacia Gum E414 And Xanthan Gum E415 (As Carrier For Food Additive) Rice Starch Natural Flavoring

FUTURALS PRO NIVEOUS AQUA

A Coloring Food Option That Is a "Clean" Label Clouding Agent in Beverages. Improved Settling Rate Vs. TIO_2

Rice Starch Emulsifier (Acacia Gum E414, Xanthan Gum E415) Natural Flavoring

Chapter 2 Methodology

2.1.Thesis Outline

The research method used for this thesis is a desk-based secondary research of peer-reviewed published research papers along with data from the government and non-governmental organization sources. A number of research papers have evaluated health implications of titanium dioxide based on ingestion and inhalation as well as the potential alternatives for titanium dioxide in food industries namely confectionery, dairy and pet food. The research question within this thesis is to investigate whether these alternatives as mentioned in the introduction would be a suitable replacement for titanium dioxide in food products, their availability and consumer acceptability and perception.

The research question will be evaluated by performing:

i. Comparative analysis of the different alternatives of Titanium Dioxide as Food additives
ii. An evaluation of the suitability as an alternative to the following food industry: confectionery, dairy and pet food
iii. Analysis of the commercial viability of these 'alternatives' for the food industry manufacturers.

2.2.Data Inclusion

The research papers that were selected the inclusion of this study were from experimental and observational studies on safety and health implication of titanium dioxide and the alternatives that are available as a replacement following on from the ban. The literature reviews that was collected were from time period 2015-2023 with historical articles from 1996 and 1987 using databases, PubMed, Science Direct, MDPI, Elsevier, Springer Nature, Wiley and Taylor and Francis.

The search string used was ((“Titanium dioxide in food” OR “Titaninum Dioxide effects in food” OR “Effect of Ingestion of Titanium Dioxide” OR “Effects of Inhalation of Titanium Dioxide” OR “Alternatives for Titanium Dioxide in food” OR “Titanium Dioxide in confectionery” OR “Titanium Dioxide in Dairy” OR “Titanium Dioxide in pet food” OR “Titanium Dioxide as a food whitener” OR “Food grade titanium dioxide ban” AND “Food grade titanium dioxide replacement”

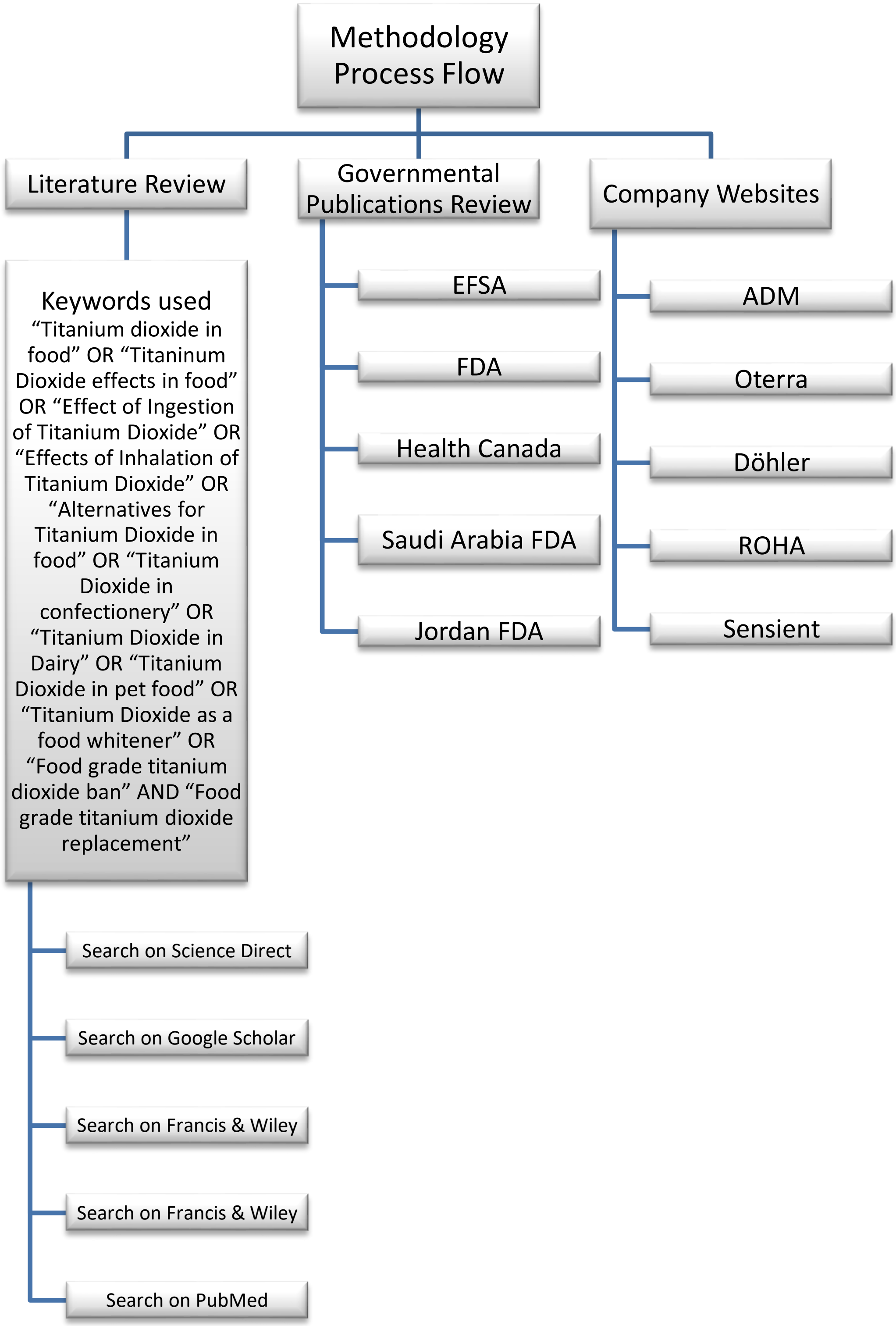


Figure 8. Represents the Methodology process flow on the secondary research using paper peer reviews journals, official governmental websites and legislations and company websites as part of the comparative studies

Chapter 3 Results

3.1. Health Implications – Ingestion

Study	Test Groups	Methods of Analysis	Main Conclusions
Shepherd et al. (1987)	N=42 resected PP's 9 Crohns, 6 UC 4 ileal lymphoma 4 inflammatory stricture 4 Colonic carcinoma, 4 intussusception 3 misc., 2 familial adenomatous polyposis, 7 postmortem cases.	Light microscopy, SEM XES	Elemental Ti pigments were detected in 34 patient samples aged 6 years or older. Additional findings indicated the presence of comparable pigments in mesenteric lymph nodes.
Powell et al. (2000a)	N= 20 resected GALT tissues 15 IBD	Laser scanning microscopy TEM	Anatase TiO_2 partic

	5 Colonic carcinom	xray microanalysis, Imaging electron energy loss spectroscopy	les ranging from 100 to 200 nanometers were observed.
Powell et al. (2000b)	N=85 cultured colonic biopsy sections 28 UC 21 Crohn's 36 controls	3 stimulants of 2000ng/ml LPS TiO2 LPS coated to TiO_2 surface IL-1 bioassay IL-1β ELISA.	Conjugation of LPS to TiO2 resulted in notable elevations of IL-1 and IL-1β in stimulated explant biopsies compared to unstimulated control samples in both UC and control groups. However, no responses were observed in Crohn's samples.
Hummel et al. (2014)	N=51 GALT tissue biopsies 62 Crohn's 26 UC 63 non-IBD	Blinded semiquantitative light microscopy	The level of pigmentation increases with age but is significantly lower in patients who have Crohn's disease.
Jones et al. (2015)	N=9 volunteers received a single dose of 5mg/kg b.w. TiO_2 nanoparticles dispersed in water.	ICP-MS	No apparent uptake of elemental Ti.
Pele et al. (2015)	N=7 volunteers with normal intestinal permeability administered	Darkfield microscopy ICP-MS	A peak in the absorption of both reflective and elemental Ti was observed six hours after ingestion.

	100mg of $fgTiO_2$		
Bettini et al. (2017)	1st series of experiments (N=10) Adult male Wistar rats. 2nd series of experiment (N=11 to 12 per group) ith (N=12 as control) 3rd series of experiment (N=4)	Confocal microscopy and micro X-ray fluorescence imaging NanoSIMS imaging Intestinal permeability measurement Cell isolation and flow cytometry analysis. Cell culture and induction of cytokine response Cytokine assays Colon cell lines and cytotoxic assay.	Food-grade TiO2 particles cross the stomach obstruction and arrive at the liver without changing digestive penetrability or causing DNA harm in Peyer's patches. Particles of food-grade TiO2 have an effect on dendritic cell frequencies and T cell populations in the Peyer's patches and cause imbalances in intestinal and systemic immune responses. Particles of food-grade TiO2 cause mucosal low-grade inflammation and initiate and promote the formation of preneoplastic lesions in the colon.
Ruiz et al. (2017)	N=56 Blood samples from 28 controls 5 active UC, 6 remission UC 8 active Crohn's disease	ICP-MS	In comparison to controls and other disease states, individuals with active UC exhibited significantly elevated levels of Ti in their blood.

	9 remission Crohn's disease.		
Farrell and Magnuson (2017)	N= 9	Transmission electron microscopy (TEM) Dynamic light scattering (DLS).	There is no accumulation of titanium in tissues following consumption of diets containing 200 ppm food grade TiO_2.
Heringa et al. (2018)	N= 15 post-mortem liver and spleen samples.	ICP- HRMS, SEMEDX	The presence of Ti was detected in the liver (measuring 86421nm) and spleen (ranging from 88 to 445nm), with roughly 24% of the total particles measuring less than 100nm.
Peters et al. (2020)	N=15 post-mortem liver, spleen, kidney, jejunum and ileum.	ICP-MS, SEM - EDX	The detected levels of Ti in tissues ranged from less than 0.01 to 2.0 mg Ti/kg, and the particulate TiO2 concentrations ranged from 0.01 to 1.8 mg Ti/kg.

Table 1. A compilation of human in vivo and in vitro studies investigating TiO_2.

Table abbreviation stated in alphabetical order. Atomic emission spectroscopy (AES), Energy dispersive xray detection (EDX), Enzyme linked immunosorbent assay (ELISA), Gut associated lymphoid tissues (GALT), High resolution mass spectrometry (HRMS), Inductively coupled plasma – mass spectrometry (ICP-MS), Interleukin (IL), Miscellaneous (Misc.), Scanning electron microscopy (SEM), Transmission electron microscopy (TEM), Ulcerative colitis (UC), X-ray energy spectroscopy (XES).

3.2. Health Implications – Inhalation

Study	Test Groups	Methods of Analysis	Main Conclusions

Ferin et al. 1992	N= 344 Fisher rats were exposed to Ti02-F or Ti02-D as aerosols in 300-liter horizontal laminar flow whole-body chambers and exposed for 6h/day , 5 days/week for up to 12 weeks and the exposure was discontinued and rats were maintained for up to 64 weeks in a filtered-air environment. Fine Titanium Dioxide		20 nm sized TiO2 particles penetrate more easily into the pulmonary interstitial space of rats than 250 nm sized TiO2 particles. Three-month inhalation exposure in rats demonstrated that the clearance of 20 nm TiO2 particles was significantly slower than that of 200 nm TiO2 particles, and more particles translocated to interstitial sites and regional lymph nodes
Grassian et al. (2007)	N=24; 6 week old male C57BI/6.	powder X-ray diffraction (XRD), transmission electron	The mice that were acutely exposed had (7.22mg/m³ NPs) which showed inflammation

	Mice were grouped in six and exposed to TiO_2 nanoparticle aerosol in a whole body exposure of two ways. Acutely for 4 hours and subacutely exposed for 4hr/day for 10 days.	microscopy (TEM), Braunner, Emmett, and Teller (BET) surface area measurements, attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and X-ray photoelectron spectroscopy (XPS)	or lung toxicity whereas mice that were subacutely exposed had higher value of 8.88mg/m^3, they undergone immediate necropsy and after 1 to 2 week post-exposure showed higher counts of total cells and macrophages in bronchoalveolar lavage (BAL) fluid compared with sentinel. By week 3, the mice recovered.
Yin et al. 2014 (2014)	N= 30; 7 week old male Kunming mice, grouped by 5 in each chamber. Allocated into 2 groups (control group and aerosol inhalation group).	ICP-MS, Light Microscopy, Blood coagulation analyser, automatic analyzer	The liver may metabolize TiO2 nanoparticles that are inhaled, and the urinary system may then eliminate them. H2O2 and maleic dialdehyde (MDA) in brain homogenate extracts clearly increased after mice were exposed to TiO2 nanoparticles. While the number of platelets (PLT) and reticulocytes (Retic) significantly increased, the number of white blood cells (WBCs) decreased. In

	Respiratory study on aerosol inhalation of 20nm anatase TiO_2. Mice were exposed in a whole-body exposure chamber with a relative concentration of (6.34 ± 0.22 mg/m^3) of inhaled TiO2 nanoparticles. The mice were then exposed for 8 hours a day for 3 weeks.		addition, the inhalation exposure group's mice had a shorter prothrombin time (PT) than the control group's mice. Additionally, the inhalation exposure group had elevated levels of ALT, AST, BUN, and CREA compared to the control group. The findings presented in this work ought to be more suitable for assessing the respiratory toxicity of nanomaterials because the whole body exposure method is a physiological exposure route.
Nurkiewicz et al. (2008)	N= 6-7 weeks old Sprague Dawley rats Whole body exposure chamber. The cage can		Animal Studies - owed that exposure to TiO2 particles may cause cardiovascular effects at concentrations below those causing adverse pulmonary effects. In rats exposed to submicron-sized TiO2 (<1 µm) or nano-sized

	accommodate 3 rats for each exposure.		TiO_2 (21 nm) at airborne exposures aimed at achieving similar particle mass deposition in the lungs (nano-sized: 1.5–12 mg/m3, 240–240–720 min; submicron-sized: 3–15 mg/m3, 480 min) they observed systemic microvessel dysfunction in the absence of pulmonary inflammation or lung damage.
Check 22, 29, 126 126 - Wang JX, Liu Y, Jiao F, Lao F, Li W, Gu YQ, et al. Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO_2 nanoparticles. Toxicology 2008; 254: 82-90.			Translocation of TiO_2 to CNS

29 - Wang JX, Chen CY, Liu Y, Jiao F, Li W, Lao F, et al. Potential neurological lesion after nasal instillation of TiO2 nanoparticles in the anatase and rutile crystal phases. Toxicol Lett 2008; 183: 72-80.			
Oberdörster et al. (1994)			reported that TiO2 NPs (21 nm) caused a greater pulmonary inflammatory response than TiO2 at same mass burden, with greater amounts of TiO2 NPs entering the alveolar interstitium in the lungs.
Study (127) Wang JX, Chen CY, Liu Y, Jiao F, Li W, Lao F,			The lung particle analyses indicated that workers exposed to respirable TiO2 had particle retention in their

et al. Potential neurological lesion after nasal instillation of TiO2 nanoparticles in the anatase and rutile crystal phases. Toxicol Lett 2008; 183: 72-80. ***(Might be too old of a study?!)***			lungs that included TiO2, silica, and other minerals, sometimes years after cessation of exposure. In most cases of tissue-deposited TiO2 was associated with a local macrophage response and fibrosis that was generally mild. In one case papillary adenocarcinoma and TiO2 associated pneumoconiosis was reported in the lung of a 53-year-old male who had been engaged in packing TiO2 for about 13 years and had 40-year smoking history.1
130 Boffetta P, Soutar A, Cherrie JW, Granath F, Andersen A, Anttila A, et al. Mortality among workers employed in the titanium dioxide production industry in Europe. Cancer			6 EU Countries adian population-based case-control study.129 The retrospective cohort lung cancer mortality study130, which included workers in the TiO2 production industry in six European countries, showed a small but significant elevation in lung cancer mortality among male TiO2 workers when compared to the general population. However, the data did not suggest an exposure-response relation.

Causes Control 2004; 15: 697-706.			
Christensen, F.M.; Johnston, H.J.; Stone, V.; Aitken, R.J.; Hankin, S.; Peters, S.; Aschberger, K. Nano-TiO2—Feasibility and challenges for human health risk assessment based on open literature. Nanotoxicology 2010, 5, 110–124. [CrossRef]			

3.3. Alternatives

Results on company – to put a table here.

Can put Countries in the table again- same as

In the intro – ensure to introduce each countries and what they are doing and find relevant resources from them

Do the same for the intro of the companies, who they are and what are they doing and where are they located, how big they are and relevant resource needed.

Discuss all the tables in the discussion section

3.4. Countries within and outside of the EU

4. Country	Banned from	Comment

European Union **FOOD**	August 7, 2022	Ban has been approved for food uses.
European Union **FEED**	June 20, 2022	Denial of authorization of titanium dioxide as a feed additive for all animal species.
Switzerland	September 15, 2022	Following the EU Ban for foods.
Gulf States (GCC)	October 21, 2022	Following the EU Ban for foods.
Saudi Arabia	October 21, 2022	Following the EU Ban for foods.
Yemen	September 25, 2022	Following the EU Ban for foods.
Israel	June 1, 2023	Following the EU Ban for foods.
Turkey	Date still unkown	Proposed to update Turkish regulations to align with updates to EU. Recent information from the TiO_2 working group states Turkey is skeptical of a ban. However, no formal information as of yet.
Jordan	June 8, 2022	Per the Jordanian Chamber of Commerce. No Import of products with TiO_2.
Israel	October 31, 2022	WTO notification. Following the EU Ban for foods. No comments yet about pharma.

Table 1. Countries that have a ban on TiO_2 adapted from

Countries Considering a ban

Country	**Comment**
Brazil	ANVISA currently evaluating, no position yet.
Argentina	ANMAT/INAL currently evaluating, no position yet.
Mercosur Countries	Regulators currently evaluating, no position yet.

Colombia	Regulators currently evaluating, no position yet.
Japan	MHLW currently evaluating, no position yet. TDMA study package sent 11 August 2022. They are neutral at this time and have no intention to take immediate action.
South Korea	MFDS currently evaluating, no position yet. Difficult to get feedback.
Russia	No plans to take action at this time, but it is expected to follow EU
Thailand	Neutral and awaiting JECFA
Qatar	Proposed ban. Now delayed implementation until April 2023. To be discussed in the region at Dubai International Food Safety Conference Nov 1-3

Table 2. Countries considering a ban

(Description of the table above) the above table contains…. The infor was combined rom online sources, from following reputable governmental bodies, websites

Countries Skeptical of the ban

Country	**Comment**
United States	US FDA confirming that their position is that the available safety studies do not demonstrate safety concerns connected to the use of titanium dioxide as a color additive.
Canada	Health Canada published Report stating that TiO2 is Safe
Australia and New Zealand	In line with the outcomes of recent reviews of EFSA opinion, conducted in the United Kingdom (UK) and Canada, Food Standards Australia New Zealand (FSANZ) found no safety concerns
UK	UK will continue use of E171. Food Standards Agency conducts independent review of EFSA opinion and risk assessment. Timeline for risk assessment to conclude: Q1 / 2023

South Africa	SA will not take any actions at this time. Use will be reviewed if JECFA has re-evaluated its safety when new evidence is available

Table 3. Countries skeptical of the ban adapted from…

4.1. Food Colour Companies and Alternatives

Company	Portfolio	Portfolio Products	Form	Application	Technology
Oterra (CHR Hansen)(2023)	CAPCOLORS ®	CAPCOLORS® White 100 WSS-P	Powder	Chewing gum Chocolate dragées	Calcium carbonate encapsulation of modified starch
Döhler(2023a)	White Diamond™	White Diamond (1µm particle size) White Diamond (4µm particle size) As per Fact Sheet	Powder	Creams in bakery Powder in beverages Hard boiled candy Pan coated confectionery	Calcium Sulphate
Sensient Food Colors (2023)	Avalanche™	Avalanche™ MB	Powder	Bakery Fillings Confectionery Dairy Dessert Instant Drinks Pet Food Plant-Based Cheese Plant-Based Meat Savoury	Mineral Based
		Avalanche™ Fusion Xtra	Powder	Confectionery Frostings Panned Applications Savoury	

		Avalanche™ Nebula	Liquid	Beverages Confectionery Dairy Dessert Sauces And Condiments Savoury Syrups	
		Avalanche™ Ultra	Powder	Beverages Dairy Instant Drinks Retort Dry Grocery Sauces And Condiments Wet Pet Food	
ADM(2023)	Pearl Edge™	Pearl Edge™ Silk	Powder	Pan Coated confectionery Compressed tablets Jelly gums Gummy candies Dairy and dairy alternative Bakery icings and fillings Soups, sauces and dressings Meat and seafood alternatives Petfood	Native Corn Starch
		Pearl Edge™ Satin	Powder		
		Pearl Edge™ Shine	Powder		
		Pearl Edge™ Shine +	Powder		
		Pearl Edge™ Star-Lite	Powder	Sugar free application	
		Pearl Edge™ Splash	Liquid	Non- alcoholic beverages	
		Pearl Edge™ Splash +	Liquid	Alcoholic beveragdes	

Roha (2023)	Niveous	Natracol Niveous Pearl	Powder	Gummies	Starches (Rice, Tapioca), Color (Calcium Carbonate E170), Sucrose Ester E473 (As Carrier for Food Additive
		Natracol Niveous Ivory	Powder	Panned Candies Gummies	(Calcium Carbonate E170) - Low cost
		Futurals Pro Niveous Rime	Powder	Panned Candies Gummies	Starches (Rice, Tapioca), Emulsifier (Sucrose Ester E473) - E number Free
		Futurals Pro Niveous Moon	Powder	Panned Candies	Starches (Rice, Tapioca) - no emulsifier
		Futurals Pro Niveous Lily	Powder	Panned Candies Gummies	Rice Starch
		Natracol Niveous Aqua	Powder	Clouding for Beverage	Color (Calcium Carbonate E170) Acacia Gum E414 And Xanthan Gum E415 (As Carrier For Food Additive) Rice Starch Natural Flavoring
		Futurals Pro Niveous Aqua	Powder	Clouding for Beverage	Rice Starch Emulsifier (Acacia Gum E414, Xanthan Gum E415) Natural

					Flavoring- E number Free

Table X Represents the Food Colour Companies and their offered range of portfolio solutions for titanium dioxide alternative. Sources taken from company websites, blogs, newsletters and food industry reliable secondary resources.

Chapter 4 Discussion

The aim of this thesis is to investigate the evolution of Titanium Dioxide (TiO_2) as a food additive, its applications into food systems and the challenges that the food industry is facing with its recent ban in the European Union.

The research question within this thesis is to investigate whether these alternatives as mentioned in the introduction would be a suitable replacement for titanium dioxide in food products, their availability, consumer acceptability and perception.

The research question has the following objectives to be evaluated by performing:

i. Comparative analysis of health implications concerning ingestion and inhalation of TiO_2.
ii. The ongoing amendments in the regulations concerning TiO_2.
iii. Comparative analysis of the different alternatives of TiO_2 as Food additives in accordance to the market availability of food industry manufacturers in order to cope with the challenges.
iv. An evaluation of the suitability as an alternative to the following food industry: confectionery, dairy and pet food.

5.1. Health Implications – Ingestion

According to the results shows in Table X (need to check tables), the studies that were conducted from 1987 up until 2020 were all via in vivo and in vitro studies in sourcing human tissue and then studies of interaction with TiO_2. Therefore, there is an absence of a 'true' human subject research as well as human control. There was also an emphasis on the nanoparticle form of TiO_2 which has been quite the focus instead of the version that is food grade type. Barreau et al. (2021) have stated that depending on the source of TiO_2, the Nano fraction has a range of 10 to 55% of fgTiO_2. The biological responses could have a variation when it comes to implications in human health when it comes to both Nano and micro particle version of TiO_2 (Pele *et al.*, 2015).

An international Organisation for Economic Co-operation and Development (OECD) is a platform where the governments of 37 democracies with market economies work together in creation of policy guidelines which helps encourage long-term sustainable economic growth. Within OECD, there are test guidelines for chemicals and their safety to protect human health (OECD, 2023).

There were three studies that were conducted in accordance with OECD health implication in terms of ingestion. First study was a duration of 90 days sub chronic toxicity, second study was repetition of dose toxicity for 28 days and third was acute oral toxicity. A study by Farrell and Magnuson (2017) demonstrated that through rat exposure of TiO_2, there was not enough distribution and excretion throughout the body. Again, the dosage of TiO_2 may not be comparable to that of human intake, however Hummel et al. (2014) have suggested that, there is build-up of fgTiO_2 in the body over a period of time and there was not a direct comparison in human being administered fgTiO_2 with dosage of 30mg/kg b.w/day for 7 days straight.

5.2. Health Implications – Inhalation

5.3. Amendments in Regulation on Titanium Dioxide

It was announced by the Swiss Federal Food Safety and Veterinary Office (FSVO) on the 09 March 2022 that Switzerland has withdrawn the authorisation of E171 as food additive with a scrutiny period of six months that has ended on 15 September 2022. ('Switzerland withdraws authorisation of E171 (titanium dioxide) in food', no date). Similarly with Saudi Arabia, the use of TiO_2 as a food additive has been assessment by Saudi Food and Drug Authority (SFDA circular FS-CIR-1-

V1/220421 and a statement has been issued that stated that all legal measure must have been taken by 21 October 2022. Yemen have also followed and has issued a decree of banning TiO_2 starting 25 September 2022. Finally, Qatar has also published a circular on the 09 September 2022 prohibiting the use of TiO_2 with a deadline of 15 October 2022 on imported products while the existing products in the market must have been already removed by the same date. **(Zotero, website).** Israel on the other hand has notified the World Trade Organisation (WTO) on amendment on the prohibition usage of TiO_2 on all type of food effective as of 1 June 2023 with adjustment to the following edition list for the Public Health Regulations of Food Additives 2001. Any food products produced until 1 June 2023 could be marketed until the expiration date. This decision was adopted from the Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to regulation (EC) No 1333/2008 of European Parliament and of the council as regards the food additive titanium dioxide (E171) **(REFERENCE).**(*Israel Notifies WTO of Amendment Regarding Titanium Dioxide | Effective from 1 June 2023*, no date)**.**

As for Turkey there was a proposal to realign the Turkish regulation to correspond with the EU regulation, however, there has not been any final decision made and an ongoing review to revisit. Therefore, the presence of TiO_2 as a colour food additive in Turkey is still predominantly found in chewing gum, confectionery and bakery products (GNPD, 2023).

The Jordan Food and Drug Administration (JFDA) has declared to put a stoppage on food product manufacturing that contain TiO_2, with the deadline being 01 January 2023 and JFDA have decided to cancel all of the permits that have been previously issued on goods import. There was also a suspension of registration of foods with special use and food supplements for athletes containing TiO_2 (https://www.one-line.com, 2022) The decision made was a proactive approach based on the decision coming from EFSA (Weather, 2022).

5.4. Overcoming Challenges by Innovation within the Food Industry Manufacturers

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Chapter 5 Conclusion and Future Work

In conclusion, there were many studies concerning NP- TiO_2 rather than fgTiO_2 targeting on investigations relating genotoxicity, carcinogenicity and immunotoxicity. This is evident in the health implications of TiO_2 when it comes to ingestion.

The legislations worldwide will continue to evolve over time and this would be highly monitored on a country by country basis, as the TiO_2 ban has only been publicly announced in 2022. Each country will have its own assessment and will continue to do so following the overall economic market. The fall of TiO_2 market in the food industry will be evident in the future, however, it is not guaranteed that this will be completely prohibited as food additive. With confectionery industry being the largest category to be affected by the ban, there were not sufficient studies in the literature regarding the alternatives as well as there is also a need for future work on the health implications per region and country as there was not enough evidence on its implications on other food categories such as dairy and pet food.

Food companies have been continuously innovating and making breakthroughs to create solutions for the ban of TiO_2. They have developed a wide range of portfolio that is sourced from different natural alternatives or food additives with mainly calcium carbonate derivatives, starches like rice, tapioca, and native and modified. There are other alternatives that could be explored in the future as well as there is a need for an oil soluble solution especially for any fat based products. So far, they is no solution for this type of food application.
There is a huge area of studies that needs to be explored when it comes to application of mentioned alternatives in the market and their performances in comparison with TiO_2.

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