Communication

Use of Food Additive Titanium Dioxide (E171) Before the Introduction of Regulatory Restrictions Due to Concern for Genotoxicity

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Abstract: Food additives are used for a variety of technological or processing reasons, including to add or restore color in a food. In the European Union (EU), the safety of food additives was in history assessed by the Scientific Committee on Food, while the role of risk accessor is not in the hands of the European Food Safety Authority (EFSA). Only additives for which the proposed uses are considered safe are on the EU list of authorized additives. Very recently, in May 2020, a scientific opinion was published by the EFSA, concluding that TiO_2 can no longer be considered as a safe food additive, and the European Commission is expected to remove it from the list of authorized food additives in the near future. Our aim was to investigate the trends in the use of TiO_2 in the food supply. A case study was conducted in Slovenia, using two nationally representative cross-sectional datasets of branded foods. The original sample contained 49,919 pre-packed food items, while analysis was performed on N=12.644 foods (6.012 and 6.632 in 2017 and 2020, respectively) from 15 food subcategories, where TiO_2 was found as a food additive. Overall, we observed a significant decrease in the use of TiO_2 (3.6% vs. 1.8%; $p<0.01$) over the course of these three years. The food containing the highest amount of TiO_2 was in the chewing gum category (36.3%) in 2017, and chocolate and sweets category (45.9%) in 2020. Meanwhile, in 2017, the largest within-category share of TiO_2-containing foods was observed in the chewing gum category, namely, 70.3%, and these products presented over 85% of the market share. In 2020, only 24.6% of chewing gums contained TiO_2, which accounted for only 3% of the market share. In conclusion, we showed an overall decrease in TiO_2 use and considerable improvements in certain food categories (particularly in chewing gum), despite the fact that this additive has not yet been officially removed from the list of authorized additives. Specific food categories (i.e., chocolate and sweets) were identified, where product reformulation is needed, and where official controls by authorities will be most relevant.

Keywords: titanium dioxide; E171; food supply; nanoparticles; safety; Europe; Slovenia

1. Introduction

Titanium dioxide (TiO_2) has been added as a white pigment to a variety of food products, including bakery products, sauces, cheese, edible ices and sweets. In addition to food, titanium dioxide is also used in medicinal products as an excipient and in personal care products as a pigment, sunscreen and thickener [1, 2].

TiO_2 was first approved for use in food in 1966 by the US Food and Drug Administration (FDA), with the stipulation that its content must not exceed 1% of the food weight [3]. On the basis of the Codex Alimentarius of the Food and Agriculture Organization/World Health Organization (FAO/WHO) [4] safety evaluation, TiO_2 has been authorized as a food additive by the European Union (EU) with code E 171 since 1969 [5]. As it was permitted for use in the EU before January 20, 2009, it belongs to the group of food additives which are subjected to a safety re-evaluation by the European Food Safety Authority (EFSA), according to Commission Regulation (EU) no. 257/2010 and in line with the provision of Regulation (EC) no. 1333/2008 [6]. Therefore, the safety of TiO_2 as a food additive was re-evaluated by the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) [7] in 2016, on the basis of which, EFSA concluded that TiO_2 did not raise concerns with respect to genotoxicity and carcinogenicity. Genotoxicity refers to the ability of a chemical substance to damage the genetic material of cells, which may lead to carcinogenic effects [8]. The EFSA also recommended that additional studies be conducted to fill the gaps in possible effects on the reproductive system, which could lead to an established Acceptable Daily Intake (ADI) for TiO_2. Therefore, in January 2017, the European Commission (EC) issued an open call for additional data for TiO_2, including reproductive toxicity data. Several studies investigated the toxicity of dietary TiO_2 [9-21], raising some concerns regarding its potential tumor-promoting activity. In 2018, the outcome of four specific studies [9, 15, 18, 20] was included in scientific evaluation, to determine the need to re-open the conclusion of the EFSA's opinion from 2016. However, the decision was taken in 2018 that the re-opening of this issue was not needed [22]. In April 2019, the French Agency for Food, Environment and Health and Safety at Work (ANSES) delivered a scientific opinion, based on 25 studies published between 2017 and 2019 [23], on the exposure to nanoparticles of TiO_2, and highlighted that the previous EFSA's assessment did not consider all available data. In response to this opinion [24], the EFSA noted that the ANSES reiterated previously identified concerns and data gaps, and did not present findings that disabled the Authority's previous conclusions on the safety of TiO_2. Furthermore, the Office for Risk Assessment and Research of the Netherlands Food and Consumer Product Safety Authority (NVWA) delivered an opinion on possible health effects of TiO_2 in 2019 [25], highlighting the possible immune and reproductive toxicological effects of TiO_2. While further activities were underway to obtain new data, the French Government followed the precautionary principle, based on the opinion of the ANSES in 2019 [23], and decided to ban TiO_2 in food products, starting on 1st January 2020. Just a few days after this decision was announced, a joint letter [26] was published to EC, with civil society organizations requesting to remove TiO_2 from the EU list of permitted food additives. Following the request of the EC in March 2020, the EFSA started an additional safety evaluation of this additive. An in-depth safety assessment report for the TiO_2 was published on 6th May 2021 [27]. The EFSA Panel concluded that with consideration of the available evidence, a concern for genotoxicity could not be excluded and, therefore, TiO_2 can no longer be considered as a safe food additive.

Food additives are an important part of processed foods. Consumers have expressed concern for some time about their possible adverse health effects [28] and would like to be better informed about their potential health implications [29, 30]. EU Member States and the EC as risk managers request EFSA to provide independent scientific advice, which informs European food policy makers. In the next step, the EFSA's scientific advice on TiO_2 will be used to support further regulatory procedures and decisions. The most realistic outcome is that the use of TiO_2 as a food additive will not be approved in the EU in the near future.

In Slovenia, food composition datasets are primarily intended for monitoring the nutritional values of food and evaluating the efficiency of food reformulation activities. While the national "Nutrition and Public Health" research program and the Food Nutrition Security Cloud project (FNS-Cloud) also enabled the collection of data on ingredients as well the use of food additives, this has not yet been prioritized and used in research. However, considering the abovementioned public health urgency, the aim of this short communication was to evaluate the prevalence and changes in the use of TiO_2 as a food additive in the food supply since 2017, when the EC issued an open call for additional toxicity data for TiO_2. The Slovenian food supply was selected for a case study, using nationally representative cross-sectional data on the composition of prepacked foods in 2017 and 2020. Assessments of the use of other food additives will follow in full papers in the future.

2. Materials and Methods

2.1. Data Collection and Categorization

The study was conducted on a sample of prepacked foods, available in Slovenia, European Union. The food supply sample was collected for 2017 and 2020 in major retailers, representing the majority of the food market, and is part of the Composition and Labelling Information System (CLAS, Nutrition Institute, Ljubljana, Slovenia) [31]. The dataset was prepared by the extraction of food labelling information from photographs of all branded foods, available in selected food stores at the time of collection. Data were collected with the aim of monitoring the nutritional composition of processed foods in the food supply [32], with adaptation, and we also collected ingredient lists. The detailed methodology of the data collection is described elsewhere [33, 34].

Foods were classified into food categories according to Global Food Monitoring Group (GFMG) recommendations [32], with minor modifications [33, 34]. Without food supplements, food additives sold to consumers in food stores and food, which did not fit into any of the GFMG food groups, our dataset contained 49,919 pre-packed food items—9,670 and 26,229 from 2017 and 2020 monitoring, respectively. We identified all foods in this dataset, where ingredient list text contained terms "TiO_2", "E 171" and/or "titanium (di)oxide".

Food (sub)categories that contained foods with added TiO_2 as a food additive at least in one sampled year and were further investigated in this study are as follows: biscuits; cakes, muffins and pastry; canned fish with vegetables; chewing gum; chocolate and sweets; cordials; desserts; flavored yogurt; ice cream and edible ices; jelly; processed fish products; side dishes; soup; spreads and processed cheese; and sugar. Our total study sample, therefore, included between 12.664 and 6.012 foods for 2017, of which 215 contained TiO_2 (3.6%), and 6.632 foods for 2020, of which 122 (1.8%) contained TiO_2.

2.2. Data Processing and Statistical Analyses

Food composition data were processed using Microsoft SQL Server Management Studio 13.0, Microsoft Analysis Services Client Tools 13.0, Microsoft Data Access Components (MDAC) 10.0, Microsoft Excel 2019 (Microsoft, Redmond, Washington, DC, USA) and the Composition and Labelling Information System (CLAS) (Nutrition Institute, Ljubljana, Slovenia). Statistical analyses were performed using Microsoft Excel 2019 (Microsoft, Redmond, Washington, DC, USA).

For statistical evaluation, we calculated proportions of TiO_2-containing foods in different food (sub)categories. Additionally, we calculated the within-category proportion of foods containing TiO_2, which was corrected with product market shares using the previously described sale-weighting approach [34]. In the investigated food categories, market share data were available for 59.8% (N=3597) and 54.2% of foods (N=3597) for 2017 and 2020, respectively. Sale-weighted proportions of TiO_2-containing foods were calculated for each (sub)category separately, using the EAN barcode as a unique product identifier, with consideration of product packaging quantity and number of sold products in a 12-month period (based on nationwide sales data provided by food retailers). Food subcategories with less than four TiO_2-containing foods were excluded from this analysis.

Descriptive analysis was used for proportions of food that contained TiO_2, and the 95% confidence interval (95%CI) was calculated employing the Wilson score interval [35]. A two-tailed z-test was used to identify differences in the use of TiO2 between 2017 and 2020. The level of significance was set at $p < 0.05$. The following subcategories were excluded from this part of the analysis due to their low sample size of foods containing TiO_2: processed fish products; canned fish with vegetable; sugar; ice cream and edible ices; desserts; flavored yogurt; cordials; soup; biscuits; side dishes and spreads and processed cheese.

3. Results and discussion

The study was conducted on a sample of 6012 foods and beverages in 2017 and 6632 foods and beverages in 2020. Within the 15 selected food subcategories, 13 categories contained TiO_2 in 2017 (215 products), and 10 categories in 2020 (122 products). In 2017, foods containing the highest amount of TiO_2 were distributed in the chewing gum category, accounting for more than a third (36.3%) of the total amount of TiO_2-containing foods (Figure 1). The second third was represented by chocolates and sweets (32.6%), followed by cakes, muffins and pastry (11.6%); jelly (8.4%); and processed fish products (2.3%). In 2020, almost half of TiO_2 was distributed in the chocolate and sweets category (45.9%); one third in the chewing gum category (27.9%); followed by cakes, muffins and pastry (9.0%); jelly (5.7%); and processed fish products (4.9%) (Figure 1). The remaining categories (each with less than a 3% share) represent 9% and 7% of TiO_2-containing foods in 2017 and 2020, respectively (Figure 1, "Other").

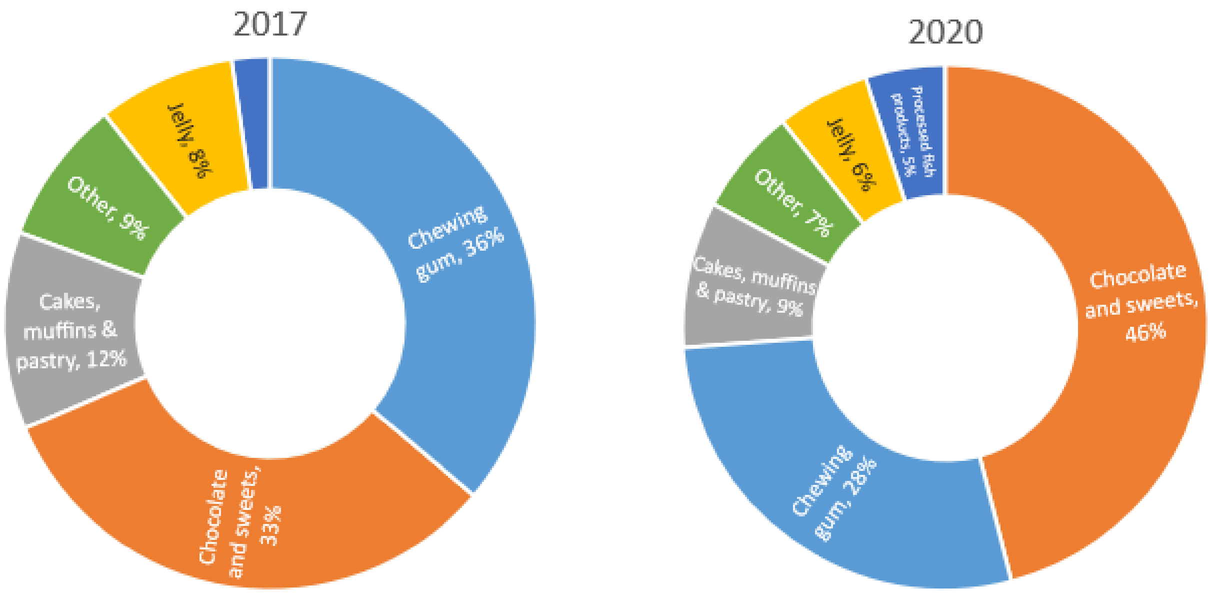

Figure 1. Distribution of foods containing TiO_2 per food (sub)category in 2017 versus 2020.

Furthermore, we calculated per-category proportions of TiO_2-containing foods in the food supply for both 2017 and 2020 (Table 1). For each year, we calculated the (non-weighted) proportion as a percentage of TiO_2-containing foods of all available foods in the category. To gain an insight into the availability of such foods with a consideration of market shares, we further employed the sale-weighting approach using nationwide 12-month sales data, provided by the largest food retailers in Slovenia. Such an approach provides information on whether TiO_2 is used in market-leading brands or mostly in niche products. It should be noted that sales data were available for most, but not all foods in our study sample (see Section 2.1 for details). Missing data mostly reflect availability in discounter retailers.

Table 1. (Sub)category proportions of foods containing TiO_2 (E171) as food additive in the food supply for 2017 and 2020 (Slovenia).

	2017				2020				Z-Test Statistic for proportions	
Food category	Total N	Added TiO_2 N	% (95% CI)	Sale-weighted proportion (%)	Total N	Added TiO_2 N	% (95% CI)	Sale-weighted proportion (%)	Proportion change (95% CI)	p- value
Chewing gum	111	78	70.3 (61.8–78.8)	85.5	138	34	24.6 (17.4 – 31.8)	3.1	45.6 (34.5-56.8)	< 0.01
Jelly	185	18	9.7 (5.5 – 14.0)	14.8	159	7	4.4 (1.2-7.6)	20.2	5.3 (0.0-10.6)	0.03
Processed fish products	71	5	7.0 (1.1– 13.0)	19.3	87	6	6.9 (1.6 – 12.2)	19.0	0.1 (-7.8-8.1)	ns
Cakes, muffins and pastry	569	25	4.4 (2.7 – 6.1)	3.0	639	11	1.7 (0.7 – 2.7)	1.1	2.7 (0.7-4.6)	< 0.01
Chocolate and sweets	1917	70	3.7 (2.9 – 4.5)	2.8	2173	56	2.6 (1.9 – 3.2)	1.1	1.1 (0.0-2.1)	0.02
Canned fish with vegetable	60	1	1.7 (0.3 – 8.9)	*	60	0				ns
Sugar	127	2	1.6 (0.4 – 5.6)	*	108	0				ns
Ice cream and edible ices	431	6	1.4 (0.3 – 2.5)	1.6	586	3	0.5 (0.0 – 1.1)	*	0.9 (-0.4-2.1)	ns
Desserts	207	2	1.0 (0.4 – 2.3)	*	298	0				ns
Flavored yogurt	419	3	0.7 (0.2 – 2.1)	*	386	0				ns
Cordials	179	1	0.6 (0.1 – 3.1)	*	190	0				ns
Soup	264	1	0.4 (0.1 – 2.1)	*	257	1	0.4 (0.1 – 2.2)	*	0.0 (-1.1-1.1)	ns
Biscuits	1035	3	0.3 (0.1 – 0.9)	*	1122	2	0.2 (0.1 – 0.6)	*	0.1 (-0.2-0.5)	ns
Side dishes	199	0			224	1	0.5 (0.1 – 2.5)	*		ns
Spreads and processed cheese	238	0			205	1	0.5 (0.1 – 2.7)	*		ns
Total	6012	215	3.6 (3.1– 4.0)	na	6632	122	1.8 (1.5-2.2)	na	1.8 (1.1-2.3)	< 0.01

Notes: Data presented for food categories with at least one product with TiO_2 in either 2017 or 2020 dataset. 95% CI: 95% confidence interval; N—number of all products; ns—not significant; na—not applicable; *—low sample size (sale-weighted proportions not calculated for subsamples with N<4).

Per-category non-weighted proportions of TiO_2-containing foods represented up to 70.3% in 2017 (Table 1). In 2017, the largest share of TiO_2-containing foods was represented by chewing gum, comprising more than two third of the sample (70.3%), followed by jelly (9.7%) and processed fish products (7.0%) (Table 1). Chewing gum was also the highest ranked category (24.6%) in 2020, followed by processed fish products (6.9%) and jelly (4.4%).

In 2017, the sale-weighted proportion of TiO_2-containing chewing gums was higher than the non-weighted proportion (85.5% vs. 70.3%), showing that this food additive was present in major brands. The situation changed considerably in 2020, when the sale-weighted proportion was much lower (3.1% vs. 24.6%). This indicates that a decrease in the use of TiO_2 was even more pronounced in the best-selling and most popular brands. However, the conclusions for other food categories are unclear, where differences between sale-weighted and non-weighted proportions were expressed to a lower extent. Beside chewing gums, food subcategories with the highest sale-weighted proportions of foods with TiO_2 were jelly (14.8%) and processed fish products (19.3%) in 2017. Considerably high sale-weighted proportions were also observed in these two categories in 2020 (20.2% and 19.0%, respectively).

The overall comparison of the 2017 and 2020 data showed a significant ($p<0.01$) decrease in the use of TiO_2 as a food additive from 2017 to 2020. Across the 15 observed food subcategories, 3.6% foods contained TiO_2 in 2017, and 1.8% in 2020. This change could be attributed to the availability of new evidence on the potential health risks of TiO_2, also followed by concerns raised by national health authority agencies [23, 25]. As health concerns were also raised by the EFSA [27], it is expected that responsible food producers will remove it from their products, despite the fact that it has not yet been officially restricted from the EU food supply. A statistically significant decrease in the use of TiO_2 was also observed in specific food categories, where TiO_2 was a relevant additive in 2017. Sale-weighted proportions showed a similar trend, with the exception of the abovementioned processed fish products and jelly.

To our knowledge, this is the first repeated cross-sectional study on the use of TiO_2 in the food supply, in which trends in the use of TiO_2 in prepacked foods was investigated with consideration of market share data. Such methodology makes the study results particularly relevant for the assessment of public health risks. While this makes comparisons with other studies difficult, relevant comparison can be performed without consideration of sale-weighting. Mintel's Global New Products Database (GNPD) [36], which contains data of newly launched foods in different countries (but not Slovenia), was used in the recent safety assessment of TiO2 by the EFSA [27]. For a more relevant comparison, we combined several of Mintel's food subcategories [37]; the highest proportion of TiO_2-containing foods was observed in chewing gums (39%), followed by pastilles, gums, jellies and chews (10%); cakes, pastries and desserts (4%); and chocolate and sweets (3%) [27]. The Mintel database cannot be considered as cross-sectional, as it only contains data on newly launched products on the market (and not the overall situation in the food supply, where some market-leading brands have a long history of availability). Nevertheless, it should be mentioned a decreasing trend in the use of TiO_2 in newly launched foods was also observed. Data are also available for the US, where TiO_2 was most commonly used in non-chocolate candy (32%), followed by cupcakes and snack cakes (14%), cookies (8%), coated pretzels and trail mix (7%), baking decorations (6%), gum and mints (4%) and ice cream (2%). However, it has been assumed that many other foods contain TiO_2, as in the US market, TiO_2 can be considered as an exempt color, which does not require explicit declaration on the ingredient statement [38].

Given the scrutiny from regulatory bodies, the food industry has been working on TiO_2 alternatives for some years. Reformulation initiatives are also stimulated by various non-governmental active groups. In the US, for example, the *As You Sow* group put pressure on the Dunkin' brand, which then withdrew the use of TiO_2 from their sugar powdered donuts [39]. However, replacing TiO_2 across all applications is technologically very challenging, as TiO_2 is not only an excellent whitening pigment, but also very cost effective

[38]. However, rice starches now offer clean label solutions that can help with reducing the chipping and cracking of coatings [38]. Avalanche, starch and mineral based white opacifier are most the common replacements for TiO_2 in food applications [40].

The strength of the study is in the use of two large nationally representative cross-sectional food composition datasets in combination with market shares. While such an approach was used in the past for the assessment of public health risks related to specific nutrients, i.e., salt [41] or sugar [34], we showed that it can be also employed for food additives. The limitation of the study is that the used dataset did not contain all available foods, and that sales data were not available for the whole dataset. However, we should mention that data collection included all major retailers with a nationwide network of food stores, and that sales data were available from retailers which are responsible for over 50% of the food market. Another limitation is that the data on the use of TiO_2 were extracted from food labels, and not determined in a laboratory. However, the regulation requires the labeling of functional additives, and the laboratory analysis of thousands of foods is not a feasible option in food supply studies. We should also note that our study did not investigate certain groups of foods, where a higher use of coloring agents could be expected, such as food supplements and food additive products, which are also available to consumers in food stores.

5. Conclusions

According to the results of our study, pre-packaged food products in Slovenia have undergone several improvements regarding the use of TiO_2 in certain food categories. In recent years, we have witnessed an increased regulatory scrutiny of TiO_2 as a food additive. In other studies, this was reflected in a decline in new launches of foods containing TiO_2, while this cross-sectional study also confirmed such an observation in a whole supply of processed foods in Slovenia. We observed that in the past, the category with the most common use of TiO_2 was chewing gums. In 2017, approximately 70% of chewing gums contained TiO_2, and these products presented over 85% of the market share (by weight). However, the situation changed drastically; in 2020, approximately 25% of chewing gums contained TiO_2, accounting for only 3% of the market share. The other two food categories with a high use of TiO_2 are jelly and processed fish products, while in other food categories, less than 3% of products contain TiO_2. Considering EFSA's 2021 announcement of TiO_2 no longer being safe to use, a further decrease in the use of this additive is expected, despite the fact that it has not yet been officially removed from the list of authorized food additives in the EU. Specific food categories were identified (i.e., chocolate and sweets), in which product reformulation is needed and official controls by authorities will be most relevant.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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