Meeting

Exposure to Titanium Dioxide in the UK population

Introduction

1. Titanium dioxide (TiO2) was an authorised Food Additive (E171) in the EU and currently remains authorised in the UK, under Retained EU Regulation No. 1333/2008 and Retained EU Regulation No 231/2012. It is used in food as a colouring to make food more visually appealing, to give colour to food that would otherwise be colourless, or to restore the original appearance of food. Titanium dioxide has been the subject of multiple safety evaluations.

2. In 2016, the EFSA Panel on Food Additives and Flavourings evaluated the safety of E171 and determined that it consisted mainly of micro-sized titanium dioxide particles, with a nano-sized (100 nm) fraction of less than 3.2% by mass. Uncertainties around the identity and characterisation of E171 were highlighted, noting that no limits for the particle size of E171 were set. Similarly, with regard to toxicity, uncertainties around the identity and characterisation of E171 were also highlighted.

3. Specifications of E171 titanium dioxide were reviewed again in 2019. Based on the fraction of nanoparticles present in E171, it was determined that the food additive fell under the scope of the EFSA guidance on nanotechnology for “a material that is not engineered as nanomaterial but contains a fraction of particles, less than 50% in the number–size distribution, with one or more external dimensions in the size range 1–100 nm”. Thus, a recommendation for re-assessment of the safety of titanium dioxide was proposed and as a result an updated EFSA Opinion was published in May 2021.

4. In this 2021 opinion, the EFSA Panel considered that some findings regarding immunotoxicity and inflammation with E171 as well as neurotoxicity with TiO2 nanoparticles may be indicative of adverse effects. They also considered that there were indications of the induction of aberrant crypt foci with E171 and that no studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO2 nanoparticles were available. Overall, on the

basis of the currently available evidence along with all the uncertainties, in particular the fact that the concern regarding genotoxicity could not be resolved, the EFSA Panel concluded that E171 can no longer be considered as safe when used as a food additive.

5. Following the publication of the EFSA Opinion, the UK's COT and Committee on Mutagenicity (COM) considered the EFSA findings, and an interim position paper was published (COT, 2022). Overall, it was observed that the percentage of absorption was reported to be higher in the 2021 opinion than in the previous evaluation (EFSA, 2016), based on the same dataset. Additionally, the COT also questioned the conclusions with regards to the ability of TiO2 to induce aberrant crypt foci. Furthermore, the findings of the studies on neurotoxicity were considered inconsistent by the COT. It was noted that the extended one generation reproduction toxicity (EOGRT) study did not report any effects and that most of the other studies on this endpoint were of nanomaterials. They considered that had the test material in the EOGRT study been dispersed and stabilised in the nano form, some effects could possibly have been observed. The COT, as previously, questioned the relevance of such dispersion to real world use. Members noted that the histopathology tests performed for the EOGRT study were standard and were not sensitive enough in comparison to other studies on this endpoint that performed specific neuro-histopathology testing.

6. With regards to genotoxicity, the COT were in agreement with the COM's view and further noted the large discrepancy between the underlying dataset and the conclusions drawn by EFSA. They further highlighted the inconsistencies between the outcomes of the 2020 Scientific Committee on Consumer Safety (SCCS) Opinion discussed in detail in paragraph 10, where it was determined that the genotoxic effects of titanium dioxide manifest either via a threshold or secondary mechanism, and the outcomes of the 2021 EFSA evaluation, where the Food Additives and Flavourings (FAF) Panel concluded that it was unclear if a threshold mode of action could be assumed. Regarding the genotoxicity of the nanoparticles, the COT considered that this could either be a concentration effect leading to oxidative damage or a stress effect, however, it was unclear as the results in different cell lines were equivocal and inconsistent. It was also noted that in some tests, titanium dioxide had shown less reactivity.

7. On balance, the Committee considered that the weight of evidence did not support the conclusions drawn by EFSA. The COT also agreed with the comments of the COM with regards to risk communication that "As it stands the conclusion is highly risk averse based on the weak evidence available, and it

might create unnecessary concern to the public." The COT suggested that the COM should independently review the database on genotoxicity and apply their Guidance on determining thresholds. When considering whether they agreed with EFSA's conclusion that no differentiation could be made with regards to size/form of titanium dioxide and different aspects of toxicity, the COT took the opinion that nanoparticles were driving the toxicity. The COM are currently assessing the genotoxicity of TiO2.

8. The full COT interim position paper is available here: Link to the TiO2 interim position paper. Considering the outputs of the discussions from the COT and the COM, the FSA has decided to launch their own review of the safety of titanium dioxide as a food additive.

9. A previous paper presented to the COT in March 2023, covered the data from the EOGRT study as well as information from the literature. The aim of this previous paper was to present the data underlying the main changes in the 2021 Opinion conclusions on toxicokinetic and absorption data, reproductive toxicity and aberrant crypt foci, developmental immunotoxicity and neurotoxicity from a recent EOGRT study and a revised literature search covering the period from 2015-2021. During this review, Members noted that EFSA had indications that when used by industry, E171 was dispersed into nanoparticles by sonication and therefore COT also considered data on materials made solely of nanoparticles for the assessment. However, this was questioned by COT Members as it was noted that pure nano titanium dioxide would lose its technical function (as it would not provide colour) and would therefore not be of use in food.

10. Also, it was noted that the size and shape of the titanium dioxide particle can affect absorption and agglomeration, however, it was also noted that some studies had some uncertainty about the mode of action. There was evidence that suggested that particles can pass into the blood brain barrier and into the placenta via passive diffusion and active uptake. However, it was unclear what form the titanium dioxide material was when it got into various organs and the duration it remained there. It was agreed that there was evidence of absorption, but there was little evidence of accumulation, reported in studies. The COT agreed that a no observed adverse effect level (NOAEL) of 1,000 mg/kg bw/day based on the EOGRT study could be used as a provisional point of departure (POD). The full COT March 2023 Discussion paper is available here: TiO2 March COT 2023 discussion paper. The Minutes for the COT's discussion on this paper are available here: COT Minutes March - Final.

11. A paper was presented to the COT in July 2023 highlighting the data underlying the main changes in the 2021 Opinion conclusions on immunotoxicity and neurotoxicity, the COT's initial conclusions on immunotoxicity and neurotoxicity, and a revised literature search covering the period from 2021-2023 on the following topics: reproductive toxicity, immunotoxicity, neurotoxicity, developmental toxicity, other toxicological effects and absorption, distribution, metabolism and excretion (ADME).

12. In 2013, EFSA collected data on the occurrence of E171 in food by means of a call for data. In response to this call, 61 use levels and 28 analytical results on E171 were submitted to EFSA by industry and Member States. The use levels covered 14 food categories (Flavoured fermented milk products including heat-treated products; dairy analogues, including beverage whiteners; edible ices; Other confectionery including breath-refreshening micro sweets; chewing gum; decorations, coatings and fillings, except fruit-based fillings; fine bakery wares; soups and broths; sauces (excluding tomato-based sauces); salads and savoury-based sandwich spreads; protein products; flavoured drinks (excluding chocolate milk and malt products); processed nuts; desserts; food supplements supplied in a solid form, excluding food supplements for infants and young children and food supplements supplied in a liquid form, excluding food supplements for infants and young children (EFSA ANS Panel, 2016).

13. This current paper presents the United Kingdom's (UK) estimated exposures to titanium dioxide via food sources. Exposures from other sources are not considered. No information on the extent and level of use of E 171 in medical products was made available to EFSA and similarly such information could not be located for the UK, therefore, its exposure from this use could not be considered. The EFSA 2020 Opinion did not consider exposure to TiO2 via cosmetic uses (e.g. toothpaste), however, for further information, this exposure assessment presents the findings on the exposure to TiO2 via toothpaste from a European country in paragraph 24.

14. The EFSA Panel on Food Additives and Nutrient sources (ANS Panel) was unable to establish a health-based guidance value (HBGV) for TiO2 due to deficiencies identified in the available toxicological data set, in particular with regards to the investigation of potential reproductive toxicity (EFSA, 2021).

15. A NOAEL and POD of 1000 mg/kg bw/day was provisionally used for risk characterisation based on findings from the EOGRTS as well as from 2 additional studies that reported no effects up to the same level (Warheit *et al*., 2015b. Lee *et al*., 2019).

Background

16. Titanium dioxide (TiO_2) is an inorganic compound which exists in nature in different crystalline forms – the anatase and rutile being the two most important.

17. Titanium dioxide was an authorised Food Additive (E171) in the EU in accordance with Annex II to Regulation (EC) No 1333/2008 in both anatase and rutile forms (Commission Regulation (EU) No 231/2012) and is still authorised under GB Food Law (retained EU law Regulation No 1333/2008 on food additives).

18. The uses of titanium dioxide are to give colour to food that would otherwise be colourless, to restore the original appearance of food and to use as a colour to make food more visually appealing. It is also used widely in cosmetics and medicines (EFSA, 2016).

19. To facilitate the UK's assessment, UK survey data was used to calculate TiO_2 exposures from food.

Sources of titanium dioxide exposure

Food

20. Titanium dioxide can be found in a number of food categories as detailed in paragraph 12, including: bakery products, soups, broths, sauces, salads, savoury based sandwich spreads and processed nuts. It is also used in confectionary, chewing gum, food supplements and cake icing (EFSA, 2016).

Medication

21. Titanium dioxide is present in most oral solid dosage forms and is a key constituent of tablet coating agents and capsule shells. Film coatings are routinely applied to compressed tablets to mask the unpleasant taste or odour of the tablet core, improve appearance or give a unique appearance, protect caregivers from contacting the active ingredient(s), aid swallowing, avoid dusting during packaging, protect the active ingredients from the environment, or modify the release of the active ingredient (Blundell et al, 2022).

Cosmetics

22. The EU Scientific Committee on Cosmetic products and Non-Food (SCCNFP) concluded that acute dermal toxicity is low and considered negligible as TiO2 is not absorbed through the skin (SCCNFP, 2000).

23. The EU Scientific Committee on Consumer Safety (SCCS) also provided an opinion on TiO2 (nano form) coated with Cetyl Phosphate, Manganese Dioxide or Triethoxycaprylylsilane as UV filters in dermally applied cosmetics, confirming the safe use in cosmetics for products intended for application on skin (SCCS, 2017).

24. Other evaluations were done on exposure via inhalation which is not relevant to exposure via an oral route (IARC, 2010 and SCCS, 2020).

25. The Secretariat identified one study which may be of relevance to personal healthcare use via the oral route. UK data have not been located, however, the following described study is from a European country. This paper aimed to estimate the oral intake of TiO2 and its nanoparticles (NP) from food, food supplements and toothpaste in the Dutch population between 2 to over 70 years old by combining data on food consumption (from the Dutch National Food Consumption Survey (DNFCS)) and supplement intake with concentrations of Ti and TiO2 NPs in food products and supplements. The TiO2 concentration in toothpaste was calculated using the average and maximum total-Ti levels in three toothpaste products. The total-Ti concentration was converted to the TiO2 concentration by multiplying with the mass difference ratio of 1.67, resulting in an average concentration of 6.13×10^3 mg TiO2/kg product, and maximum concentration of 9.3×10^3 mg TiO2/kg product. An additional intake via ingestion of toothpaste was estimated for children between 2 - 6 years old. The mean long-term intake to TiO2 from food products, food supplements and toothpaste (only children 2–6 years old) ranged from 0.67 mg/kg bw/day in children (2 - 6 years old), 0.17 mg/kg bw/day in people between 7 - 69 years old, and 0.06 mg/kg bw/day in people over 70 years old in the Dutch population. The estimated mean intake of TiO2 NP ranges from 2.16 µg/kg bw/day in young children, 0.55 µg/kg bw/day in 7–69-year-old people, to 0.19 µg/kg bw/day in the elderly (70+ years). The ninety-fifth percentile values were around 3.9-, 2.9-, and 1.9- fold higher than the mean values, respectively. Overall, with the highest mean long-term intake of TiO2 being 0.67 mg/kg bw/day for children aged 2-6 years it was concluded that toothpaste dominated the contribution of TiO2 NP dietary intake in young children (57%) (Rompelberg, *et al.*, 2016).

Exposure Assessment

26. Food consumption data from the National Diet and Nutrition Survey (NDNS) (Bates, 2014; 2016; Roberts 2018; Bates, 2020) and the Diet and Nutrition Survey of Infant and Young Children (DNSIYC) (Department of Health, 2013) were used to estimate exposure to titanium dioxide. Maximum occurrence levels of titanium dioxide for specific food items, reported by EFSA (2021), were also used in the estimation of exposure (Table 1). Food categories were created by the FSA Exposure Assessment Team (EAT) using data from NDNS and DNSIYC to reflect those created by EFSA for the Food Additive Intake Model and as presented in Annex II of Regulation (EC) No 1333/2008, part D. Foods in NDNS and DNSIYC were matched to food categories associated with the regulation on food additives to enable an assessment of exposure based on maximum levels reported by industry for titanium dioxide and those reported in the scientific literature. Assessments were carried out in Crème which is the software used by the FSA EAT to conduct exposure assessments.

27. Occurrence data used were those reported in EFSA, 2021 and were obtained from industry as reported by the Dutch National Institute for Public Health and the Environment (RIVM) and also levels reported in analytical studies. These levels are presented in Table 1 for sixteen food categories, although titanium dioxide is approved in many other food categories (forty-eight in total). For the exposure assessment, only use levels for these sixteen food categories were taken into account, as no data were available for the other categories and it was not possible to use the maximum permitted levels (MPLs) for TiO2 as they were established at quantum satis, rather than a specific value being ascribed. The assessment was based on maximum use levels reported to provide conservative scenarios of exposure for the population groups considered (Table 2).

Table 1: Occurrence levels of titanium dioxide (E 171) used in the exposure assessment scenarios (mg/kg or mg/L as appropriate)

EFSA Food category number	Food category name	Concentration levels used in the exposure assessment (Maximum reported)	MPL (mg/L or mg/kg as appropriate)

01.4	**Flavoured fermented milk products including heat-treated products***	**48**	**QS**
01.5	Dehydrated milk as defined by Directive 2001/114/EC	-	QS
01.6.3	Other creams	-	QS
01.7.1	Unripened cheese, excluding products falling in category 16.	-	QS
01.7.3	Edible cheese rind	-	QS
01.7.4	Whey cheese	-	QS
01.7.5	Processed cheese	-	QS
01.7.6	Cheese products, excluding products falling in category 16	-	QS
01.8	**Dairy analogues, including beverage whiteners***	**125**	**QS**
03	**Edible ices***	**857**	**QS**
04.2.4.1	Fruit and vegetable preparations, excluding compote	-	QS

04.2.4.1	Fruit and vegetable preparations, excluding compote	-	QS
04.2.5.3	Other similar fruit or vegetable spreads	-	QS
05.2	**Other confectionery including breath-refreshening microsweets***	**4,500**	**QS**
05.3	**Chewing gum***	**16,000**	**QS**
05.4	**Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4***	**20,000**	**QS**
06.3	Breakfast cereals	-	QS
06.5	Noodles	-	QS
06.6	Batters	-	QS
06.7	Pre-cooked or processed cereals	-	QS
07.2	**Fine bakery wares***	**318**	**QS**
08.3.3	Casings and coatings and decorations for meat	-	QS

09.2	Processed fish and fishery products, including molluscs and crustaceans	-	QS
09.2	Processed fish and fishery products, including molluscs and crustaceans	-	QS
09.2	Processed fish and fishery products, including molluscs and crustaceans	-	QS
09.2	Processed fish and fishery products, including molluscs and crustaceans	-	QS
09.3	Fish roe	-	QS
12.2.2	Seasonings and condiments	-	QS
12.4	Mustard	-	QS
12.5	**Soups and broths***	**193**	**QS**
12.6	**Sauces***	**4,000**	**QS**
12.7	**Salads and savoury-based sandwich spreads***	**3,000**	**QS**
12.9	**Protein products, excluding products covered in category 1.8***	**5,000**	**QS**

13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)	-	QS
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)	-	QS
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009	-	QS
14.1.4	**Flavoured drinks***	**70**	**QS**
14.2.3	Cider and perry	-	QS
14.2.4	Fruit wine and made wine	-	QS
14.2.5	Mead	-	QS
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	-	QS
14.2.7.3	Aromatised wine-product cocktails	-	QS

14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol	-	QS
15.1	Potato-, cereal-, flour- or starch-based snacks	-	QS
15.2	**Processed nuts***	**7,000**	**QS**
16	**Desserts, excluding products covered in categories 1, 3 and 4***	**200**	**QS**
17.1	**Food supplements supplied in a solid form, excluding food supplements for infants and young children***	**26,950**	**QS**
17.2	**Food supplements supplied in a liquid form, excluding food supplements for infants and young children***	**QS**	

QS – quantum satis (no maximum numerical level is specified, and substances will be used in accordance with good manufacturing practice, at a level not higher than is necessary to achieve the intended purpose and provided the consumer is not misled).

* the 16 food categories used in the exposure assessment.

28. Exposure assessments were carried out for the following population groups: Infants, toddlers, other children, adolescents, adults and the elderly.

There are two toddler groups. One group represents ages 1 - 1.5 years and the data used were from DNSIYC as this survey covers infants and young children aged 4 - 18 months (1.5 years). The other toddler group covers ages 1.5 - 3+ years and data were obtained from the NDNS, as this survey covers all age groups from 1.5 years. The mean and 95th percentile estimates are presented for each population group and food category in mg/kg bw/day in Table 2. The reported data are consumer-based, meaning that only subgroups of the population that consumed these categories of food were considered.

Table 2: Estimated mean and 95th percentile (P95) exposures (mg/kg bw/day) to titanium dioxide E 171 from its use as a food additive based on the maximum reported use level. The reported data are consumer-based.

Food group	**Infants** (4 – 11 months) **Mean (P95a)**	**Toddlers** (1 - 1.5 years) **Mean (P95a)**	**Toddlers** (1.5 - 3 years) **Mean (P95a)**	**Children** (4 - 10 years) **Mean (P95a)**	**Adolescents** (11 - 18 years) **Mean (P95a)**	**Adults** (19 - 64 years) **Mean (P95a)**	**Elderly** (≥65 years) **Mean (P95a)**
1.4-Flavoured fermented milk products including heat-treated products	0.24 (0.6)	0.2 (0.49)	0.16 (0.4)	0.097 (0.23)	0.05 (0.12)	0.044 (0.11)	0.049 (0.11)
1.8. Dairy analogues and whitener	0.91 (1.9)	1.6 (5.6)	1.9 (5.7)	0.63 (2.3)	0.21 (0.78)	0.15 (0.47)	0.18 (0.75)
12.5. Soups and broths	0.45 (1.5)	0.53 (1.7)	0.55 (1.3)	0.37 (0.94)	0.23 (0.56)	0.21 (0.54)	0.24 (0.64)

12.6. Sauces	4 (14)	4 (12)	3.5 (11)	3.3 (9.2)	2.2 (6.1)	1.7 (5)	1.4 (3.8)
12.7. Salads and savoury based sandwich spreads	2.2 (9.4)	3 (12)	2.9 (9.2)	1.9 (4.6)	0.92 (2.7)	0.95 (2.7)	0.94 (2.9)
12.9. Protein products	14 (55)	27 (190)	38 (160)	11 (49)	5.3 (18)	5.3 (18)	7.6 (30)
14.1.4. Flavoured drinks	0.15 (0.53)	0.35 (1.1)	0.47 (1.4)	0.44 (1.2)	0.4 (1)	0.24 (0.73)	0.12 (0.32)
15.2. Processed nuts	1.3 (4.6)	2.1 (8.1)	2.8 (9.9)	2 (7.2)	1 (3.6)	1.2 (3.9)	1.2 (3.4)
16. Desserts excluding products covered in categories 1, 3 and 4	1.2 (3.2)	1 (2.6)	0.64 (1.8)	0.33 (0.85)	0.14 (0.38)	0.11 (0.28)	0.15 (0.4)

17.1. Food supplements supplied in a solid form, excluding for infants and young children	1.4 (3.3)	1.7 (2.7)	1.9 (4.2)	1.1 (2.6)	0.82 (1.3)	0.95 (2.1)	0.85 (2.2)
17.2. Food supplements in a liquid form, excluding for infants and young children	3.9 (16)	3.2 (12)	3.3 (11)	1.4 (4)	3.2 (9)	1.7 (5.6)	0.91 (2.3)
3. Edible ices	0.88 (2)	1.1 (3)	1.3 (3.3)	1 (2.5)	0.55 (1.5)	0.32 (0.74)	0.35 (0.84)
5.2. Other confectionery and sweets	1.2 (2.9)	2.7 (6.9)	2.6 (7)	2.4 (7.6)	1.5 (4.7)	0.79 (2.9)	0.54 (1.8)
5.3. Chewing gum	0 (0)	1.5 (1.5)	0.73 (1.6)	0.6 (1.7)	0.57 (2.2)	0.41 (1.2)	0.63 (0.82)
5.4. Decorations, coatings and fillings, except 4.2.4	6 (16)	7.2 (19)	6.8 (17)	6.6 (18)	3.8 (10)	2.3 (6)	2.3 (6.3)

7.2. Fine bakery wares	0.3 (0.9)	0.5 (1.4)	0.6 (1.5)	0.55 (1.3)	0.3 (0.76)	0.21 (0.55)	0.23 (0.57)
Total**	3.9 (14)	6.9 (19)	11 (26)	9.5 (24)	5 (13)	3.7 (10)	3.3 (9.1)

*Estimates are rounded to 2 significant figures.

**Determined from a distribution of individual total exposure or consumption of any combination of categories rather than by summation of the respective individual mean/95th percentile consumption values for each of the food categories.

a 95th percentile exposures have been reported for the UK to aid the comparison with data reported by EFSA.

Table 3: A summary of the estimated mean and 95th percentile total exposures to titanium dioxide E171 in the representative population groups.

Age group	**Mean exposure (mg/kg bw/day)**	**95th percentile exposure (mg/kg bw/day)**
Infants (4 – 11 months)	3.9	14
Toddlers (1 – 1.5 years)	6.9	19
Toddlers (1.5 - 3 years)	11	26
Children (4 - 10 years)	9.5	24
Adolescents (11 - 18 years)	5	13

Adult (19 - 64 years)	3.7	10
Elderly (≥65 years)	3.3	9.1

29. Table 3 shows that the mean total exposures to titanium dioxide from use as food additives in the sixteen categories considered, ranged from 3.3 mg/kg bw/day in the elderly to 11 mg/kg bw/day in toddlers. The 95th percentile exposures ranged from 9.1 mg/kg bw/day in the elderly to 26 mg/kg bw/day in toddlers (aged 1.5 - 3 years). When compared to the EU-wide dietary exposures reported by EFSA (Table 4), the UK estimates fall within the range presented for the EU. The mean exposure estimated for UK infants (3.9 mg/kg bw/day) was close to the upper range reported by EFSA (3.6mg/kg bw/day). EFSA data covers infants from 3 months old, and the UK data covers infants from 4 months old.

Table 4: Estimates reported by EFSA for a maximum reported levels exposure scenario for TiO2. Data are derived from EU dietary surveys.

Age group	**Mean exposure (mg/kg bw/day)**	**P95 exposure (mg/kg bw/day)**
Infants (3 -11 months)	0.06 – 3.6	0.2 – 15.8
Toddlers (1 – 2 years)	0.9 – 12.8	2.9 – 31.4
Children (3 - 9 years)	1.9 – 11.5	5.9 – 31.3
Adolescents (10 - 17 years)	1.3 – 6.2	4.0 – 18.6
Adults (18 - 64 years)	0.7 – 6.7	2.4 – 15.9
The elderly (65+ years)	0.4 – 4.9	1.9 – 12.7

30. The food categories contributing most to exposure were considered using population-based estimates of exposure.

31. In table 5, the food categories contributing most to the exposure to titanium dioxide are sauces, decorations, coatings and fillings; desserts; and protein products which mostly consists of alternatives to animal products such as milk and meat.

Table 5: The highest contributing food groups to mean exposure estimates to titanium dioxide in the UK population.

Age group	Main contributor	Second main contributor	Third main contributor
Infants (4 – 11 months)	Sauces	Dessert	Protein products
Toddlers (1 – 1.5 years)	Sauces	Protein products	Desserts
Toddlers (1.5 - 3 years)	Protein products	Sauces	Decorations, coatings and fillings
Children (4 - 10 years)	Sauces	Decorations, coatings and fillings	confectionary
Adolescents (11 - 18 years)	Sauces	Decorations, coatings and fillings	confectionary
Adult (18 - 64 years)	Sauces	Protein products	Decorations, coatings and fillings
Elderly (≥65 years)	Sauces	Protein products	Decorations, coatings and fillings

Assumptions and uncertainties

32. The exposure assessment takes into account use levels in only sixteen food groups whereas, E171 is approved in more categories (forty-eight). This may introduce underestimations for exposures. However, not all foods within the categories assessed will contain E171, which means exposure in those categories may be overestimated. In addition, the assessments are based on the assumption that all food in these categories contain E171 at the maximum reported levels. It is unlikely that all foods in each category assessed will contain E171 and at the maximum reported levels. This assumption may overestimate exposure.

33. There are differences between the granularity of food groups used by EFSA for the purposes of their exposure assessment, and those used here for the UK population. This could introduce uncertainties about the comparability of the data.

34. Exposure assessments reported here are based on more recent UK data, taking into account NDNS years that reflect the period 2008 – 2019, whereas estimates reported in EFSA (2021) contains NDNS years that are relevant to 2008 - 2011.

35. The standard age groups used in the FSA are somewhat different to those used by EFSA, for instance infants are aged 3 months to 12 months, while the UK has data for infants aged 4 to 12 months. EFSA's Toddler category uses ages from 12 months and up to 3 years, but the FSA considers them to be from 12 months and up to 4 years. In addition, data for toddlers in the UK are derived from two separate surveys. These differences could introduce uncertainties when comparisons are made.

Margin Of Exposure (MOE) calculations

36. During the March 2023 meeting, the COT provisionally established a NOAEL of 1000 mg/kg bw/day for titanium dioxide. This was based on discussion of both the Warheit *et al* and Lee *et al* reproductive toxicity studies as well as the EOGRT study. The top dose used in the Warheit study was 1000 mg/kg/ bw and the titanium dioxide particles were characterised. It was noted that there were no adverse effects in the oral gavage study by Lee *et al* and the NOAEL was reported as 1000 mg/day for both. The COT also considered the potential aberrant crypt foci effects of titanium dioxide. It was noted that the EORGT study showed no adverse effects in reproduction and development and there was no increase in aberrant crypt foci at titanium dioxide concentrations up to 1000 mg/kg bw. Based on the EOGRT, the COT agreed on a provisional point of departure of 1000

mg/kg/bw and stated that it seemed reasonably robust for the reproductive effects of TiO2, however, it was noted that sections of the study were due to be repeated in 2023 (COT, 2023).

37. Currently, there is no Health Based Guidance Value (HBGV) established for titanium dioxide. Therefore, to facilitate discussion, the Secretariat has used the provisional NOAEL established by the COT to provide some indicative MOE calculations to the Committee. The following calculations are based on the assumption that the evaluation of the genotoxicity of titanium dioxide will not conclude a concern for genotoxicity, and therefore the POD for risk assessment would be based on one of the other systemic endpoints.

Table 6: The Margin of Exposures (MOE) to titanium dioxide E171 in the representative population groups

Age group	**Margin of Exposure**	**95th percentile Exposure**
Infants (4 - 11 months)	256	71
Toddlers (1 – 1.5 years)	145	53
Toddlers (1.5 - 3 years)	91	38
Children (4 - 10 years)	105	42
Adolescents (11 - 18 years)	200	77
Adult (18 - 64 years)	270	100
Elderly (≥65 years)	303	110

Discussion

38. In summary, this paper presents an exposure assessment for TiO2 in the UK population. This was done by utilising DNSIYC and NDNS data. The DNSIYC survey covers infants and young children (4 months to 1.5 years) and the NDNS survey reflects the years 2008 – 2019 and covers all age groups from 1.5 years and older. Mean exposures ranged from 3.3 mg/kg bw/day in Elderly (≥65 years) to 11 mg/kg bw/day in Toddlers (1.5 - 3 years). 95th percentile exposures ranged from 9.1 mg/kg bw/day in Elderly (≥65 years) to 26 mg/kg bw/day in Toddlers (1.5 - 3 years).

39. It should be noted that personal care products such as toothpaste will add a small increment to total exposure. See the Rompelberg et al., 2016 study (paragraph 25) for more details. As the COT has yet to comment on this study, it has not been considered in the exposure evaluations.

40. To facilitate discussions the Secretariat utilised the provisional NOAEL of 1000 mg/kg bw/day for titanium dioxide from the EOGRT study to provide MOE calculations for the COT's consideration, based on the dietary exposure values. This was on the assumption that the evaluation of the genotoxicity of TiO2 will not conclude a concern for genotoxicity. The resulting MOE's ranged from 91 in Toddlers (1.5 - 3 years) to 303 in the Elderly (≥65 years). 95th percentile exposures ranged from 38 in Toddlers (1.5 - 3 years) to 110 in the Elderly (≥65 years).

Questions for the Committee

The Committee are asked to consider the following questions:

i. What are the Committee's views on the exposure assessment?

ii. Assuming that the POD for the risk assessment of titanium dioxide can be based on the systemic toxicity endpoints, does the Committee consider that an HBGV should/could be established on the basis of the provisional NOAEL?

a. If yes, what uncertainty factors should be used for the derivation of the HBGV?

b. Alternatively, does the Committee consider that the MOE approach should be used for risk assessment; and what is the threshold that should be utilised in determining the outcome of the risk assessment?

iii. The study by Rompelberg is the only study that the Secretariat were able to find with data from oral exposures other than diet. Do the Committee want this

included as a comparison for dietary intakes in the statement or just a sentence to confirm that there are not enough suitable data to determine exposures from oral sources other than dietary?

iv. Does the Committee have any other comments?

Secretariat

August 2023

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