Table 12: Summary of dietary exposure to E 171 from its use as a food additive in the maximum level exposure assessment scenario and in the refined exposure scenarios, in six population groups (minimum–maximum across the dietary surveys in mg/kg bw per day)

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
• Mean	0.06–3.6	0.9–12.8	1.9–11.5	1.3–6.2	0.7–6.7	0.4–4.9
• 95th percentile	0.2–15.8	2.9–31.4	5.9–31.3	4.0–18.6	2.4–15.9	1.9–12.7
Refined exposure assessment scenarios						
Brand-loyal scenario						
• Mean	0.05–3.5	0.8–10.0	1.7–9.7	1.1–5.0	0.6–5.5	0.4–4.2
• 95th percentile	0.1–14.3	2.6–28.0	5.2–25.4	3.3–14.9	2.0–13.1	1.7–10.4
Non-brand-loyal scenario						
• Mean	0.03–2.9	0.6–6.0	0.9–6.9	0.6–3.6	0.3–3.8	0.2–2.8
• 95th percentile	0.1–9.9	1.9–27.5	2.5–23.7	1.6–13.2	1.2–9.5	0.9–7.1

bw: body weight.

In the *maximum level exposure assessment scenario*, mean exposure to E 171 from its use as a food additive ranged from 0.06 mg/kg bw per day in infants to 12.8 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 0.2 mg/kg bw per day in infants to 31.4 mg/kg bw per day in toddlers.

In the *brand-loyal refined exposure assessment scenario*, mean exposure to E 171 from its use as a food additive ranged from 0.05 mg/kg bw per day in infants to 10.0 mg/kg bw per day in toddlers. The 95th percentile of exposure ranged from 0.1 mg/kg bw per day in infants to 28.0 mg/kg bw per day in toddlers. In the *non-brand-loyal scenario*, mean exposure ranged from 0.03 mg/kg bw per day in infants to 6.9 mg/kg bw per day in children. The 95th percentile of exposure ranged from 0.1 mg/kg bw per day in infants to 27.5 mg/kg bw per day in toddlers.

It can be noted that for infants, toddlers, children and adolescents, the maximum of the range of dietary exposure calculated is higher than in the 2016 EFSA ANS opinion. This is due to one dietary survey which was recently included in the EFSA Comprehensive database.

For the *food supplements consumers only* (results reported in Appendix T), mean exposure to E 171 from its use as a food additive ranged from 0.8 mg/kg bw per day for adults to 11.7 mg/kg bw per day for children. The 95th percentile ranged from 3.1 mg/kg bw per day for the elderly to 41 mg/kg bw per day for children.

The main food categories contributing to the exposure to E 171 are presented in Appendix U. In the non-brand-loyal exposure assessment scenario, the main contributing food categories for infants, toddlers and adolescents were fine bakery wares, soups and broths and sauces; they were soups and broths, sauces and salads and savoury-based sandwich spreads for children, adults and the elderly. Processed nuts were also a main contributing food category for adults and the elderly (Appendix U).

An exposure estimate for E 171 considering data from scientific publications (Weir et al., 2012; Taboada-López et al., 2019) was also performed. The six additional food categories considered were unripened cheeses (FC 01.7.1), processed cheeses (FC 01.7.5), breakfast cereals (FC 06.3), rice (FC 06.7), surimi (FC 09.2) and snacks (FC 15.1). Levels of E 171 for these foods were based on analytical data and were low compared to use levels reported for the other food categories. It is uncertain if products from these additional food categories are available on the European market, and therefore, the relevance of the data is unclear. However, even taking these six additional food categories into consideration resulted in only a small increase in the calculated dietary exposure to E 171 (up to an additional 0.01 mg/kg bw per day for some populations groups) (Appendix V). Some publications reported levels of E 171 in foods where E 171 is not authorised to be added in the EU (e.g. raw cows milk, fresh milk, long-life milk, plain yoghurt (Rompelberg et al., 2016); chocolate products, ripened cheese,(Weir et al., 2012) and seafood products (Yin et al., 2017). As these are not authorised uses in the EU, these levels were not considered in the above assessment.

Uncertainty analysis

In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 13.

Table 13: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/–
Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Correspondence of reported use levels and analytical data to the food items in the EFSA Comprehensive Database: uncertainties to which types of food the levels refer	+/–
Uncertainty in possible national differences in use levels of food categories	+/–
Occurrence data: – use levels considered applicable to all foods within the entire food category, whereas the average percentage of food products in the EU labelled as containing E 171 was only 1% of all the food products in the subcategories in Mintel in which E 171 is listed – not fully representative of foods on the EU market	+ +/–
The 16 food categories which were taken into account in the refined exposure assessment scenarios out of all authorised food categories (N = 48), corresponded to different percentage, depending on the food categories (32%–96% of the amount (gram of foods by body weight) of food consumption documented in the EFSA Comprehensive Database)	–
Food categories included in the exposure assessment: no data for certain food categories which were therefore not considered in the exposure estimates (n = 32/48)	–
Maximum level exposure assessment scenario: – exposure calculations based on the maximum reported use levels (reported use from industries)	+
Refined exposure assessment scenarios: – exposure calculations based on the maximum or mean levels (reported use from industries)	+/–

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

E 171 is authorised in four food categories and listed among the food colours of Group II authorised in other 44 food categories (Table 10).

In the current exposure assessment, 16 food categories were considered in the maximum level and in the refined scenarios. These food categories are the main food categories in terms of consumption levels. The Panel calculated that out of the foods authorised to contain E 171 according to Annex II to Regulation (EC) No 1333/2008, 32–96% of the amount of food consumed (by weight) per population group was reported to potentially contain E 171 as a food additive.

The Panel noted that information from the Mintel's GNPD (Appendix R) indicated that 49 out of 86 food subcategories, categorised according to the Mintel's GNPD nomenclature, in which E 171 was labelled were included in the current exposure assessment. These 49 food subcategories represented approximately 95% of the food products labelled with E 171 in the database. Furthermore, the percentage of foods per subcategory labelled to contain E 171 was maximally about 52% in sticks, liquids and sprays (on average, the percentage of food products in the EU labelled as containing E 171 was 1% of all the food products included in the subcategories in Mintel in which E 171 is listed) (Appendix R), while in the assessment, it was assumed that 100% of the foods belonging to an authorised food category contained the food additive.

Given these observations, the Panel considered overall that the uncertainties identified resulted in an overestimation of the exposure to E 171 from its use as a food additive according to Annex II to Regulation No 1333/2008 for all scenarios.

Oral exposure via other sources

E 171 is widely used as an excipient in medicinal products (Section 3). No information on the extent and level of use of E 171 in medicinal products was made available to EFSA and, therefore, its exposure from this use could not be considered. Exposure to TiO_2 via cosmetics (e.g. toothpaste) is not considered in this opinion.

4.4.4. Exposure to TiO_2 NPs from the use of E 171

Number-based particle size distributions of a series of pristine E 171 food additives and of E 171 particles extracted from food products have been reported (EFSA FAF Panel, 2019; Verleysen et al., 2020, 2021; Geiss et al., 2021). In these publications, the size and shape of isolated constituent particles and of constituent particles in aggregates and agglomerates were measured by image analysis of representative transmission electron micrographs using ellipse fitting. The short (a-axis) and long axes (c-axis) of the ellipse fitted to the 2D projection of each constituent particle was measured as a proxy of its minimal and maximal external dimension, respectively. Assuming that the particles are prolate ellipsoids (a axis = b axis < c axis), the volume (V) of each particle was estimated as $V = {}^4/_3 \cdot \pi \cdot a^2$ c and the mass (M) of each particle was calculated as $M = V \phi$, with ϕ = the density of the particles (3.89 g/cm^3 for anatase and 4.32 g/cm^3 for rutile particles). More information on the analysis of E 171 is available in the report of a project focusing on the development of analytical methodologies that allow identification and characterisation of nanoparticles in food additives in their pristine state and in simple food matrices (Verleysen et al., 2021). Using this methodology, the mass and number percentages of particles in different samples of E 171 were calculated (also Appendix W; reported in Verleysen et al., 2021).

Taking into account the available data (Verleysen et al., 2021), it can be presumed that the mass of constituent particles below 100 nm could be up to 30%, where the mean of the 12 analysed samples is 25%. The Panel noted that different types of E 171 are used in food and the percentage by number of constituent particles below 100 nm can range from 5% (rutile) to around 50% (EFSA FAF Panel, 2019). The use levels of the different types of E 171 are unknown, and therefore, it is not possible to estimate accurately the exposure to nanoparticulate TiO_2 from the use of E 171 (Table 12).

5. Uncertainty considerations

The Panel, after evaluating the scientific evidence available, has identified uncertainties related to the following points:

- The size distribution of the particles in marketed E 171 that consumers are exposed to, related to the different types of E 171, as presented in the EFSA FAF Panel (2019) opinion.
- The processes used by industry when using E 171 in food and to what extent these processes may affect the degree of agglomeration and thus internal exposure.
- State of agglomeration i.e. presence of 'free' (non-agglomerated) particles of tested material in GIT of the animals and its effect on absorption.
- Representativity of different tested materials used in toxicity and genotoxicity studies for the food additive E 171 when used in food.
- Differences in the physico-chemical properties of the different tested materials and the extent of their impact on the observed results.
- Interference in the measurements of Ti/TiO_2 in blood, tissues or organs with the most widely used analytical technique, i.e. ICP-MS, and its impact on the reliability of tissue concentration data.
- Confidence in the limited kinetic data as the basis for estimating half-lives and accumulation and for assessment of internal exposure and, related to that, the extent of systemic availability.
- None of the rodent studies were sufficiently long to cover the time needed for reaching the steady state for accumulation and this impacted the interpretation of the study results.
- Relative contribution of different molecular mechanisms leading to the production of ROS resulting in the genotoxicity of TiO_2 (inflammation, interaction with mitochondria, intrinsic potential of TiO_2 to generate ROS).
- Several modes of action for the genotoxicity may operate in parallel. The relative contributions of different molecular mechanisms elicited by TiO_2 particles are unknown; it is unclear if a threshold mode of action could be assumed.
- Nature of the interactions between DNA and TiO_2 particles leading to conformational changes in DNA

Due to large amount of information that needed reviewing in the limited time available, a structured uncertainty analysis in line with the EFSA Guidance on Uncertainty Analysis in Scientific Assessment (EFSA Scientific Committee, 2018b) was not possible. However, the Panel took a conservative approach in reaching the final conclusions.

In relation to the exposure assessment (Section 4.4.3), the Panel considered that the uncertainties identified resulted in an overestimation of the exposure to E 171 from its use as a food additive according to Annex II to Regulation No 1333/2008 for all scenarios.

6. Discussion

The safety of E 171 was re-evaluated by EFSA in 2016 in the frame of Regulation (EU) No 257/2010, as part of the re-evaluation programme for food additives authorised in the EU before 20 January 2009 (EFSA ANS Panel, 2016). On the basis of the information available at that time, the EFSA ANS Panel considered that E 171 mainly consisted of micro-sized TiO_2 particles, with a nano-sized (< 100 nm) fraction less than 3.2% by mass. Uncertainties around the identity and characterisation of E 171 were however highlighted, noting that no limits for the particle size of E 171 were set in the EU specifications. The ANS Panel concluded that, based on the data available at that time, E 171 when used as a food additive did not raise concern with respect to genotoxicity and that it was not carcinogenic after oral administration. Taking into account the presumed limited absorption of TiO_2, the ANS Panel concluded that, based on a margin of safety (MoS) calculated from the no-observed-adverse-effect level (NOAEL) of 2,250 mg TiO_2/kg bw per day (identified from a carcinogenicity study in rats) and the exposure, calculated based on the reported use levels and analytical data, E 171 would not be of concern. However, given the toxicological data set at that time, the ANS Panel identified data gaps and uncertainties that required follow-up by the European Commission by means of a call for data aimed at gathering information from IBOs. In particular, in order to address concerns related to the lack of adequate data on reproductive and developmental toxicity, the ANS Panel recommended that an EOGRT study be performed. An EOGRT study was commissioned by IBOs and its study protocol was later amended to accommodate the investigation of additional parameters related to the occurrence and TiO_2-related induction of ACF in the colon, which are preneoplastic lesions that had been reported by Bettini et al. (2017) shortly after the completion of the ANS Panel re-evaluation of E 171.

Subsequent to the evaluation of data submitted by IBOs on the characterisation of E 171 used as a food additive in the EU, the Panel recommended that the EU specifications for E 171 include the parameter of median minimum external dimension by particle number should be higher than 100 nm, measured by electron microscopy, which is equivalent to less than 50% of constituent particles by number with a minimum external dimension below 100 nm (EFSA FAF Panel, 2019).

Based on the presence of a fraction of nanoparticles in E 171, the food additive falls under the scope of the EFSA Guidance on nanotechnology, which was broadened in its 2018 revision to cover also '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' (EFSA Scientific Committee, 2018a).

For the reason given above, the proposed amendment to the specifications of the food additive E 171 (EFSA FAF Panel, 2019) was accompanied by a recommendation by the Panel for a re-assessment of the toxicological data set in line with the data requirements specified in the EFSA Guidance on nanotechnology (EFSA Scientific Committee, 2018a).

Scientific criteria for implementing the provisions of the EFSA Guidance on nanotechnology (EFSA Scientific Committee, 2018a) and specific information on the characteristics of TiO_2 nanoparticles were considered when preparing the advice from the ccWG Nano. The advice elaborated on the NSC and adaptations related to specific aspects of study design with TiO_2 which are adequate for a hazard identification and hazard characterisation of small particles, including nanoparticles (Appendix E). Following this advice (Appendix E), toxicokinetic and toxicity studies were scored for NSC (dispersion and/or confirmation of internal exposure). The confidence for assessing the toxicological effects of the fraction of small particles, including nanoparticles was as follows:

- Scoring 1 for NSC: the study is suitable.
- Scoring 2 for NSC: the study has some limitations.
- Scoring 3 for NSC: the relevance of the results cannot be verified.
- Scoring 4 for NSC: the relevance of the results is low.

As mentioned above, the characterisation of E 171 was previously evaluated by the Panel who noted that E 171 currently contains nanoparticles at different percentages (EFSA FAF Panel, 2019). Moreover, from samples of E 171 or in E 171 extracted from foods the percentage by number of particles below 30 nm is in the order of 1% or less (Verleysen et al., 2020, 2021; Geiss et al., 2021, Appendix W) Therefore, the Panel considered that studies performed with TiO_2 NPs that predominantly consist of particles smaller than 30 nm (e.g. P25) are of limited relevance to the safety assessment of E 171. However, data from toxicity studies performed with TiO_2 < 30 nm have been considered for completeness of the database and may be relevant with respect to whether a minimum limit for particle size should be included in the EU specifications for E 171.

The Panel considered that E 171 has a low oral systemic availability, probably not higher than 0.5% (Section 4.1.2). It may pass the placenta and be transferred to the fetus. Rat studies showed long half-lives for TiO_2 NP (7–90 nm) (roughly 200–450 days), a potential for accumulation (accumulation factor of 290–450) and a long time to reach steady state (3–5 years) could be estimated from these studies. The oral systemic availability of TiO_2 NP was low (most probably < 1%) but higher than for E 171. In tissues from deceased subjects, TiO_2 particles were identified in liver, spleen, kidney and intestinal tissues. The low Ti amount of the investigated organs indicated low oral systemic availability of TiO_2 ingested from a number of sources, including dietary exposure to E 171.

The Panel noted that none of the studies were sufficiently long to cover the time needed for reaching the steady-state for accumulation. Therefore, the Panel considered that this could contribute to the uncertainty for the interpretation of the toxicological findings.

In mice, no adverse effects associated with general toxicity were observed up to 1,000 mg E 171/kg bw per day, the highest dose tested, for dosing durations up to 90 days (Han et al., 2020a, scoring 2 for NSC). Also in rats, no adverse effects associated with general toxicity were observed in the EOGRT study with E 171 (Documentation provided to EFSA No 1) (scoring 4 for NSC) at doses up to 1,000 mg/kg bw per day (Section 4.2). In rat toxicity studies with TiO_2 NPs or TiO_2 containing a fraction of nanoparticles, having different duration (14–90 days), no adverse effects were observed up to the highest dose tested (from 40 to 100 mg/kg bw per day). Overall, in a weight of evidence consideration, no adverse effects associated with general toxicity were observed in rats orally exposed to E 171, TiO_2 NPs or TiO_2 containing nanoparticles.

In mice orally exposed to TiO_2 NPs < 30 nm for up to 90 days, some effects were reported, which by their nature could be adverse. However, mild hyperbilirubinaemia was not accompanied by any in liver enzymes (Yang et al., 2017); the effect size of increased fasting glycaemia and impaired glucose tolerance (Hu et al., 2015) was not accompanied by changes in insulin or other changes in lipid metabolism and therefore was not of toxicological relevance. Histopathological changes were reported in the heart (Yu et al., 2016), however, these findings were not supported by incidences and severity scores. Histopathological findings indicating inflammation were reported in the liver but investigations to confirm hepatic injury were not performed (Hong et al., 2016).

In rats orally exposed to TiO_2 NPs < 30 nm, inconsistent and/or unexplained sex differences in some parameters were reported (e.g. hypobilirubinaemia in females (Chen et al., 2015a); heart rate and blood pressure changes in females (Chen et al., 2015b); leucocyte changes in females (Heo et al., 2020); higher absolute pituitary weights in males (Heo et al., 2020); lower blood insulin levels in females, lower C-peptide levels in males and differences in blood concentrations compared to controls in a glucose tolerance test in males (Chen et al., 2020b).

The Panel considered that the effects reported in mouse studies with TiO_2 NPs < 30 nm could be associated with accumulation of NPs in various tissues, whereas inconsistent findings in rats were considered incidental.

No effects of E 171 on sexual function and fertility in either male or female rats, and on pre- and postnatal developmental were observed in the EOGRT study with E 171 (Documentation provided o EFSA No 1, scoring 4 for NSC) up to 1,000 mg/kg bw per day, the highest dose tested (Section 4.2.7). No other reproductive or developmental toxicity studies performed with E 171 have been identified from the published literature that were considered sufficiently reliable (see Appendix H). No maternal and developmental effects were observed up to 1,000 mg/kg bw per day, the highest dose tested, in a single rat developmental toxicity study with five different TiO_2 materials, TiO_2 NPs or TiO_2 containing a fraction of nanoparticles (Warheit et al., 2015b) (scoring 4 for NSC).

In mice, the effects of TiO_2 NPs < 30 nm on the testis (decreased weight, decreased seminiferous tubule diameter, germ cell apoptosis) and sperm (decreased sperm counts and motility, increased percentage of abnormal spermatozoa) were observed in three studies (Khorsandi et al., 2016, 2017; Karimi et al., 2019) at doses ranging from 50 to 300 TiO_2 NPs mg/kg bw per day. In a mouse study by

Lu et al. (2020), no effects were observed at the lowest dose tested, 10 mg/kg bw per day (scoring 4 for NSC). In rats, administration of TiO_2 NPs (21 nm) did not show effects at any dose level in a developmental toxicity study up to 1,000 mg/kg bw per day (Lee et al., 2019) (scoring 3 for NSC).

No neurotoxicity studies performed with E 171 have been identified from the published literature that were considered sufficiently reliable (see Appendix C). Based on the results of the EOGRT study in rats with E 171 (Documentation provided to EFSA No 1, scoring 4 for NSC), the Panel considered that E 171 had no adverse effects on neurofunctional endpoints in F1 cohort 2A offspring up to 1,000 mg/kg bw per day (Section 4.2.8).

TiO_2 NPs orally administered to rats during embryofetal and early postnatal development reduced hippocampal neurogenesis with TiO_2 NPs (< 100 nm) at 100 mg/kg bw per day exposure (Ebrahimzadeh et al., 2017), and dosed to adult rats produced adverse effects in the brain consistent with indications of oxidative stress with TiO_2 NPs (90 nm) at 500 mg/kg bw per day (Kandeil et al., 2019).

After oral dosing with TiO_2 NPs < 30 nm, adverse effects in both adult and developing mouse and rat brain were observed in studies identified from the published literature. Most of these effects are possibly related to oxidative stress. In mice, the Panel noted that the reduced volume of the polymorph layer of the hippocampal dentate gyrus and reduced density and number of dentate gyrus granular neurons reported by Rahnama et al. (2020, scoring 4 for NSC) with TiO_2 NPs (21 nm), is consistent with the behavioural effects reported by Zhang et al. (2020, scoring 3 for NSC), i.e. increased open field anxiety-like behaviour and unaffected spatial learning and memory. Ventral dentate gyrus is associated with anxiety behaviour, CA regions with spatial learning/memory (Eagle et al., 2016; Anacker et al., 2018). In adults rats, the most sensitive endpoint in the evaluated studies was reduced brain cholinesterase activity and increased brain Na/K-ATPase activity with TiO_2 NPs (21 nm) at a dose of 0.5 mg/kg bw per day in females dosed for 14 days (Canli et al., 2020, scoring 4 for NSC).

The Panel noted that inhibition of cholinesterase activity by nanoparticles other than TiO_2, both metal and plastic, has been reported in a number of species (Prüst et al., 2020). Since oxidative stress-related inflammation is generally associated with increased and not decreased cholinesterase activity (Corrêa Mde et al., 2008; Vaknine and Soreq, 2020), it is unclear whether there is a link between TiO_2-induced oxidative stress and TiO_2-induced decrease in cholinesterase activity.

For neurotoxicity, adverse effects were seen with TiO_2 NPs < 30 nm. In mice, Zhou et al. (2017), reported adverse effects (i.e. inhibited dendritic outgrowth, increased autophagy and oxidative stress and reduced mitochondrial function) in *ex vivo* hippocampal neurons of weanling mice after dosing TiO_2 NPs (6–7 nm) during gestation and early lactation at a dose of 1 mg/kg bw per day, the lowest dose tested. In adult female rats (Canli et al., 2020), adverse effects (reduced brain cholinesterase activity, and increased brain Na/K-ATPase activity) were observed with TiO_2 NPs (21 nm) at 0.5 mg/kg bw per day, the lowest of three doses tested, in a 14-day study. The Panel noted that Canli et al. (2020) was scored 4 for NSC.

In the immunotoxicity cohort of the EOGRT study with E 171 (Documentation provided to EFSA No 1, scoring 4 for NSC), a slight, but statistically significant decrease (–9%) in antigen specific IgM level was measured at the highest dose tested (1,000 mg/kg bw per day) in males, but without an apparent dose response. Due to technical limitations in this part of the study, it is currently not possible to conclude on the developmental immunotoxicity of E 171 (Section 4.2.9).

From other studies identified from the published literature with E 171, the Panel concludes that these studies suggest an immune dysregulatory activity of E 171, evidenced by several immune-related and inflammatory markers.

In the Han et al. (2020a) 90-day study, effects on GM-CSF and IgM and were observed following exposure to E 171, however the Panel noted the lack of a dose response, the magnitude of the effect was small that did not allow a firm conclusion given the natural variability in the parameters measured. It should be noted that in three single dose level studies with E 171 inflammatory effects were noted at lower doses, i.e. 2, 5 and 10 mg/kg per day, respectively, in rats (Bettini et al., 2017) and in mice (Urrutia-Ortega et al., 2016; Talamini et al., 2019).

Effects of E 171 may, at least in part, stem from the activity of the fraction of the smaller TiO_2 particles, as studies with these particles also indicate inflammatory effects of exposure to TiO_2 NPs (5–6 nm) at 2.5 mg/kg per day (Yu et al., 2016).

Although not a requirement in the OECD TG 443, an evaluation of ACF in the colon of satellite F0 animals was investigated in the EOGRT study (Section 4.2.6). From this study (scoring 4 for NSC), the Panel considered that oral exposure to E 171 at doses up to 1,000 mg/kg bw per day did not induce

ACF in the colon. Two additional studies reporting information on ACF were identified from the literature search. From the study by Bettini et al. (2017) (scoring 1 for NSC), previously reviewed by the ANS Panel (EFSA ANS Panel, 2018), the Panel considered that E 171 at a dose of 10 mg/kg bw per day may induce ACF per se. In addition, E 171 enhanced ACF formation after pretreatment with a genotoxic carcinogen (i.e. DMH) in rats. From a more recent study (Blevins et al., 2019) (scoring 3 for NSC), the Panel noted that no changes in the number of ACF and ABC were observed due to E 171 exposure alone. However, limitations in the pathological examination of ABC and ACF (sampled colon area limited; technical issues with fixation) precluded a conclusion by the Panel on any potential for ABC and ACF formation. Dietary E 171, with or without treatment with DMH, had no effect on the length of the colonic glands examined or the number of goblet cells/unit.

Overall, the Panel noted that the effect of E 171 alone (without prior initiation) in producing ACF reported by Bettini et al., has not been replicated in later investigations (EOGRT and Blevins et al., 2019), but one of these investigations (Blevins et al., 2019) had methodological limitations. Furthermore, it is unclear to what extent animals were exposed to NPs in the EOGRT and Blevins et al. (2019). The Panel considered that E 171 may induce ACF in male rats at a dose of 10 mg/kg bw per day when it is dispersed in test vehicle preventing agglomeration of NPs prior to administration. The Panel noted that there is literature indicating that ACFs may be a risk factor for human colorectal cancer (Anderson et al., 2012; Drew et al., 2018; Quintanilla et al., 2019; Hong et al., 2019; Clapper et al., 2020; Kowalczyk et al., 2020; Siskova et al., 2020).

No new publications on chronic toxicity or carcinogenicity have been identified in the literature search. During the re-evaluation of E 171 in 2016, the ANS Panel had evaluated a carcinogenicity study in mice and rats (NCI, 1979), performed with TiO_2 mixed with the diet. The ANS Panel had concluded that the study indicated that TiO_2 was not carcinogenic in rats and mice. However, in the current opinion, the Panel considered that this study was not appropriate to ascertain the absence of a potential to elicit chronic toxicity and carcinogenicity by TiO_2 nanoparticles.

A number of studies, considered to be reliable by the Panel, have examined or included analyses of GIT microbiota changes in response to exposure to E 171, TiO_2 NPs and TiO_2 NPs $<$ 30 nm. There is no consensus on quantifying the extent of GIT microbiota changes and when such changes should be considered adverse. Therefore, the Panel was unable to come to any conclusion regarding the effects of E 171 on GIT microbiota and related effects on health.

Combining the available lines of evidence, the Panel considered that TiO_2 particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. The Panel noted that the largest particle sizes resulting in genotoxicity after oral exposure were TiO_2 (160 $\pm$ 59 nm) in an *in vivo* comet assay (Sycheva et al., 2011) and TiO_2 NPs (58 $\pm$ 8 nm) in *in vivo* MN and CA assays (Chakrabarti et al., 2019). Negative results were observed in two studies with particles of similar or larger size, i.e. in an *in vivo* MN assay with TiO_2 NPs (75 $\pm$ 15 nm) (Chen et al., 2014) and in an *in vivo* comet assay with E 171 reported by the authors to be distributed in three size groups of particles as observed from the TEM images (135 $\pm$ 46 nm, 305 $\pm$ 61, 900 $\pm$ 247 nm) but without quantitative information of each side group (Jensen et al., 2019). The Panel noted that the ranges of the particles sizes in studies resulting in a positive or negative outcome were overlapping, the number of negative studies performed with large particles is low. Accordingly, a cut-off value for TiO_2 particle size with respect to genotoxicity could not be identified. The Panel also considered that no clear correlation was observed between other physico-chemical properties of TiO_2 NPs, such as crystalline form, shape and agglomeration state and the outcome of genotoxicity assays.

The relative contribution of the MOAs, which may operate in parallel, to the resulting genotoxicity of TiO_2 is unknown and there is uncertainty on whether a thresholded mode of action could be assumed. Even if it was assumed that all potential modes of action would be indirect, the available data would not allow identification of a threshold dose. Therefore, the Panel concluded that a concern for genotoxicity of TiO_2 particles cannot be ruled out.

Considering the technical data, including heterogeneous information on particle size of E 171, as provided by IBOs during the re-evaluation of this food additive (EFSA ANS Panel, 2016), the ANS Panel considered that the highest reported percentage value of 3.2% of nanoparticles ($<$ 100 nm) by mass, could be used as an estimate of NPs in E 171. In contrast, the current data (Verleysen et al., 2020) suggest E 171 can contain about 30% of nanoparticles $<$ 100 nm by mass. Therefore, in the current assessment, the Panel took into consideration the principles established in the EFSA Guidance on Nanotechnology (2018). In addition, a literature review was performed for the current assessment that also captured studies performed specifically with TiO_2 NPs. Data on the potential genotoxicity of TiO_2 – that was not previously identified as relevant based on the available information on maximum

percentage value of nanoparticles present in E 171 for the 2016 re-evaluation of E 171 – were also included in the current assessment.

7. Conclusions

Concerning the content of nanoparticles in E 171, the Panel considered that:

- according to the Regulation EU (No) 231/2012, there is currently no limitation for the content of nanoparticles in E 171.
- according to data received from interested business operators, less than 50% of constituent particles in E 171 have a minimum external dimension below 100 nm by number (EFSA FAF Panel, 2019).
- the percentage by number of constituent particles below 30 nm was in the order of 1% or less in samples of pristine E 171 or in E 171 extracted from foods analysed after dispersion.
- TiO_2 particles in pristine E 171 likely form large agglomerates. When dispersion procedures are applied, these agglomerates may deagglomerate, resulting in increased numbers of 'free' nanoparticles. The extent of agglomeration and number of 'free' nanoparticles present may be further affected by the conditions in food and the GIT environment.

Accordingly, the Panel concluded that studies with TiO_2 nanoparticles were relevant in the current risk assessment of E 171. However, studies performed with TiO_2 NPs that predominantly consisted of particles smaller than 30 nm were considered to be of limited relevance.

Concerning absorption and toxicity of TiO_2 particles that are present in E 171, the Panel concluded that:

- the absorption of TiO_2 particles is low, however they can accumulate in the body due to their long half-life;
- studies on general and organ toxicity, including the newly performed EOGRT study with E 171, did not indicate adverse effects up to a dose of 1,000 mg/kg bw per day. Also, no effects were seen in studies retrieved from the literature with TiO_2 NP > 30 nm up to the highest dose tested of 100 mg/kg bw per day;
- no effects on reproductive and developmental toxicity up to a dose of 1,000 mg/kg bw per day, the highest dose tested, were observed in the EOGRT study with E 171. No other reliable studies were found in the literature addressing these effects with E 171;
- some findings regarding immunotoxicity and inflammation with E 171 as well as neurotoxicity with TiO_2 NPs may be indicative of adverse effects;
- there are indications of the induction of aberrant crypt foci with E 171;
- no studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO_2 nanoparticles were available;
- combining the available lines of evidence on genotoxicity, TiO_2 particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. No clear correlation was observed between the physico-chemical properties of TiO_2 particles – such as crystalline form, size of constituent particles, shape and agglomeration state – and the outcome of either *in vitro* or *in vivo* genotoxicity assays;
- a concern for genotoxicity of TiO_2 particles that may be present in E 171 could not be ruled out
- several modes of action for the genotoxicity may operate in parallel. The relative contributions of different molecular mechanisms elicited by TiO_2 particles are unknown and there is uncertainty whether a threshold mode of action could be assumed;
- a cut-off value for TiO_2 particle size with respect to genotoxicity could not be identified.

Overall, on the basis of all currently available evidence along with all the uncertainties, in particular the fact that genotoxicity concern could not be ruled out, the Panel concluded that E 171 can no longer be considered as safe when used as a food additive.

This conclusion applies to E 171 as described in Commission Regulation (EU) No 231/2012 as well as to E 171 specified in the EFSA FAF Panel (2019).

Documentation provided to EFSA

1) LPT (Laboratory Pharmacology and toxicology), 2020a. Interim Report - EOGRT study of Titanium dioxide E171-E in rats by oral administration via the diet. Report No. 36222.

Submitted by the European Commission on 27 May 2020; updated version of the report submitted by Titanium Dioxide Manufacturers Association on 1st September 2020

2) LPT (Laboratory Pharmacology and toxicology), 2020b. Dietary Analysis - EOGRT study of Titanium dioxide E 171-E in rats by oral administration via the diet. Report No. 36222, Submitted by the European Commission on 14 September 2020.
3) Global Pathology Support D.V, 2020. Pathology assessment - EOGRT study of Titanium dioxide E 171-E in rats by oral administration via the diet (Draft amendment to final pathologist report). Test site reference no. 523/LPT Report No. 36222, Submitted by the European Commission on 15 September 2020; Draft amendment to final pathologist report submitted by Titanium Dioxide Manufacturers Association on 16 November 2020; update submitted 08 January 2021.
4) Fraunhofer Institute for Molecular Biology an Applied Ecology, 2020a. Determination of titanium in rat blood and urine of an EOGRT study with Titanium Dioxide E 171-E. Study number: U-EBR-244/6-27, Submitted by the European Commission on 16 September 2020.
5) Fraunhofer Institute for Molecular Biology an Applied Ecology, 2020b. Validation: Digestion of Titanium dioxide E 171-E in rat blood samples and determination of dissolved titanium in digested samples. Submitted by the European Commission on 16 September 2020.
6) Fraunhofer Institute for Molecular Biology an Applied Ecology, 2020c. Validation: Digestion of Titanium dioxide E 171-E in rat urine samples and determination of dissolved titanium in digested samples. Submitted by the European Commission on 16 September 2020.
7) Finish Institute of occupational health (FIOH), 2013. Facilitating the safety evaluation of manufactured nanomaterials by characterising their potential genotoxic hazard Project Coordinator French Agency for Food, Environmental and Occupational Health & Safety (ANSES) report. In vitro testing strategy for nanomaterials including database. Final report, March 2013. Submitted by FIOH, October 2020.
8) French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 2013. Nanogenotox, Deliverable 5: In vitro testing strategy for nanomaterials including database. Final report, March 2013. Submitted by ANSES, October 2020.
9) National Research Centre for the Working Environment (NRCWE), 2013 NANOGENOTOX work package six report, Comet and Micronucleus in vivo data. Submitted by NRCWE, November 2020.
10) Federal Institute for Risk Assessment (BfR) 2012. BfR study reports of the comet for TiO_2 NP as part of the work package five of the Nanogenotox project. Submitted by BfR, November 2020.
11) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 16th and 18th November 2020.
12) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 7 January 2021.
13) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 12 January 2021.
14) BioReliance, 2020a. Bacterial Reverse Mutation Assay. Submitted by Titanium Dioxide Manufacturers Association, 12 January 2021.
15) BioReliance, 2020b. In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL). Submitted by Titanium Dioxide Manufacturers Association, 12 January 2021.
16) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 22 January 2021.
17) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 29 January 2021.
18) Additional clarifications submitted in response to a request from EFSA. Submitted by Titanium Dioxide Manufacturers Association, 09 February 2021.

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