

Research in Food Safety
Luxembourg
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Titanium dioxide (E 171): update on EFSA's activities

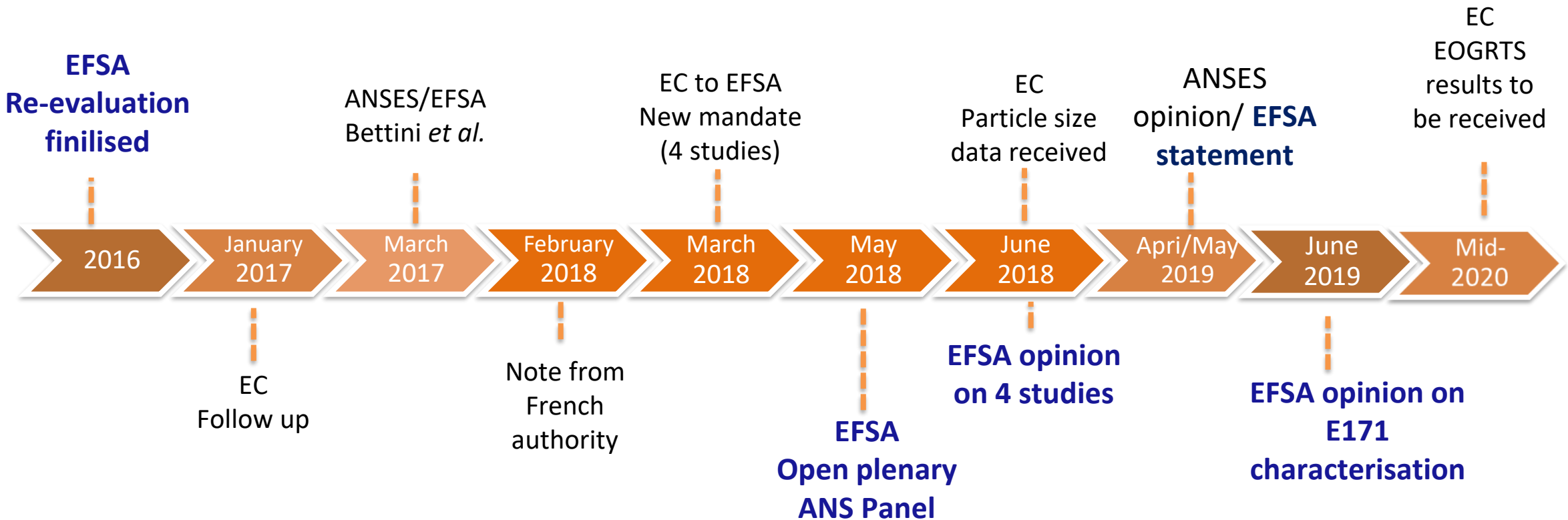
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- EFSA re-evaluation of titanium dioxide (E 171), 2016
- EFSA assessment of four publications (e.g. Bettini et al.), 2018
- ANSES assessments on E 171 (2017; 2019)
- EFSA opinion on characterisation of E 171 (2019)
- Ongoing activities

Titanium dioxide (E 171) timeline



EFSA Panel on Food Additives and Nutrient Sources added to Food (2016):
<https://www.efsa.europa.eu/en/efsajournal/pub/4545>

MAIN CONCLUSIONS

- Titanium dioxide as a food additive did **not** raise a genotoxic **concern**.
- The lowest no observed adverse effects level (**NOAEL**) of 2,250 mg titanium dioxide/kg body weight (bw) per day for males from the rat carcinogenicity study, **the highest dose tested, was identified**.
- Unable to reach a definitive conclusion on the reproductive and developmental toxicity endpoint, **no ADI established**.
 - The margin of safety (MoS) calculated from the NOAEL of 2,250 mg titanium dioxide/kg bw per day, and the exposure calculated from the reported use/analytical levels of titanium dioxide (E 171): **not considered as of concern**.
 - Once definitive and reliable data on the reproductive toxicity of E 171 are available, the full dataset would enable the Panel to establish a health-based guidance value (ADI).

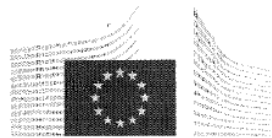
RECOMMENDATIONS- FOLLOW UP from the EC (call for data, 2017)

- **Data on particle size and particle size distribution:** submitted in 2018.
EFSA Opinion on E171 characterisation (June, 2019)
- **Dietary Extended One-Generation Reproductive Toxicity Study** with E171 food-grade titanium dioxide in rats, including cohort 1 (extension by mating of F1 animals to the F2 generation), cohort 2 (for developmental neurotoxicity) and cohort 3 (for developmental immunotoxicity).
 - **Ongoing:** to be submitted in Mid 2020

- **March 2017** → ANSES assessed the impact of the **Bettini et al. 2017** study
- **Collaboration with ANSES**
- **ANSES technical hearing** with the authors of the study
- **Joint meetings** between ANSES and EFSA experts
- **ANSES conclusion: no need to reopen the EFSA Opinion**



- The European Commission sent a **mandate** to EFSA requesting the assessment of four studies published after the publication of the 2016 ANS Panel opinion, in accordance with Article 29 (1)(a) of the Regulation (EC) No 178/2002, and indicating whether these studies would merit to reopen the existing opinion.



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Food and feed safety, innovation
Director

Brussels, 22.03.2018
SANTE.E2/AP7/km (2018)1605112
Ares (2018)1583962

Dear Dr Url,

Subject: Request for a scientific opinion from the European Food Safety Authority in relation to four new studies on the potential toxicity of titanium dioxide used as a food additive (E 171)

- Bettini et al., 2017
- Heringa et al., 2016
- Proquin et al., 2017
- Guo et al., 2017

considered in the context of the conclusions of the EFSA opinion of 2016.

- Note from the French authorities sent to the EC on 15 February 2018 requesting interim protective measures (in accordance with Article 53 of the General Food Law) to address the uncertainties in respect of the impact on human health of titanium dioxide in food.
- Implementation of measures for suspension of the placing on the market or use of the food additive titanium dioxide (E171) in all food of European origin and measures for suspension of imports of all food containing that food additive from third countries.

- Based on the **Bettini et al. study (2017)**, and the negative results of the NCI (1979) carcinogenicity studies in mice and rats, new findings not sufficient to raise a concern on the potential initiation or promotion properties of TiO₂ (E 171) on colon carcinogenesis;
- Not enough justification for a new carcinogenicity study (large number of animals), but that if additional mechanistic studies provided useful information on the relevance of the reported results, this could be reconsidered in future;
- Determination of **biomarkers for putative preneoplastic lesions** in the colon, as an additional parameter to be examined in the ongoing extended one generation reproductive toxicity study.

- the new in vitro findings in the study by **Proquin et al. (2017)** did not modify the conclusion on the genotoxicity of TiO_2 as stated in the previous EFSA opinion (EFSA ANS Panel, 2016) on the safety of TiO_2 (E171) when used as a food additive;
- the effects of engineered TiO_2 nanoparticles reported by the **Guo et al. (2017)** study were of uncertain biological significance and therefore of limited relevance for the risk assessment of the food additive TiO_2 (E171);
- there was significant uncertainty in the risk assessment performed by **Heringa et al. (2016)**, which did not include a weight of evidence analysis of the whole database.

- Overall, the four studies evaluated, highlighted some concerns but with uncertainties, therefore their relevance for the risk assessment was considered limited and further research would be needed to decrease the level of uncertainties.
- Altogether, the Panel concluded that the outcome of the four studies *did not merit re-opening the existing opinion of EFSA related to the safety of titanium dioxide (E 171) as a food additive.*

What did the EFSA ANS Panel recommend?

- in order to substantiate the observations in the Bettini et al. (2017), biomarkers for putative preneoplastic lesions in the colon as additional parameters should be examined in the extended one generation reproductive toxicity study recommended by EFSA (EFSA ANS Panel, 2016);
- further studies on TiO₂ NP should include administration in a food matrix.

- EFSA was requested to provide urgent scientific and technical assistance regarding the review of the risk related to the exposure to the food additive titanium dioxide (E 171) published by ANSES on 15 April 2019

EFSA was requested to consider whether the ANSES review

- included **new and major findings** showing that titanium dioxide (E 171) used as a food additive, is of safety concern and thus overrules the conclusions from previous EFSA opinions:
 - 2016, ANS Panel re-evaluation of titanium dioxide (E 171)
 - 2018, ANS Panel evaluation of four new studies
- Identified **further uncertainties** which are worth addressing in addition to the aspects for which follow up work is currently ongoing

- In agreement with the previous recommendation from the EFSA ANS Panel in 2016, ANSES has re-iterated the need for a precise **physico-chemical characterisation** with respect to the particle size of titanium dioxide used as a food additive.
 - As a follow-up of the 2016 re-evaluation, interested business operators have submitted new data
 - EFSA evaluated these data in order to propose a modification of the EU specifications for E171 that will define the titanium dioxide used as a food additive in food (EFSA FAF Opinion, 2019)

- ANSES opinion made reference to the gap in the **reproductive toxicity database** previously identified by EFSA in the course of the re-evaluation of titanium dioxide (E 171) in 2016 and 2018 (EOGRT study, still ongoing)
- ANSES supported the conclusions stated by the review by Charles et al. (2018) on nano titanium dioxide and recommended **new *in vivo* genotoxicity** data to be generated

- No new **carcinogenicity** studies with E171 have been identified in the literature review conducted by ANSES
- ANSES reiterated its 2017 recommendation to further investigate the **tumour promoting potential** of E 171 in the colon
 - As a follow up of 2017 ANSES and 2018 EFSA recommendations new data are being generated by interested business operators
 - Modification to the ongoing EOGRT to include measurement of ACF in the colon
 - A subchronic (100-day) dietary study with E 171 to investigate the effects of administration of E 171 on the formation of ACF in the intestine and on dendritic and T Cell tissue distribution and function with and without pretreatment with 1,2-dimethylhydrazine → Study has been completed by the Michigan State University (MSU) and University of Nebraska Medical Center [Blevins et al., 2019]

- The latest ANSES opinion published in April 2019 did not identify any major new findings that would overrule the conclusions made in the previous two scientific opinions on the safety of titanium dioxide (E 171) as a food additive issued by the EFSA ANS Panel in 2016 and 2018
- The latest ANSES opinion reiterated the previously identified uncertainties and data gaps, which are currently being addressed in the context of the follow up activities originating from the previous EFSA evaluations and their recommendations
- In addition to the aspects for which the follow up work has been finalised in June 2019 and the one currently ongoing, ANSES recommended further investigation of *in vivo* genotoxicity.

- **Term of Reference:** to provide a scientific opinion to confirm that the analytical data provided by interested parties adequately support the proposed amendment of the specifications of the food additive titanium dioxide (E 171), with respect to the inclusion of additional parameters related to its particle size

- The Panel concluded, after reviewing the available data, that a **specification of more than 100 nm**, measured by EM and taking into account measurement uncertainty, **for median minimal external dimension**, equivalent to less than 50% for the percentage of constituent particles by number with a median minimal external dimension below 100 nm, should be inserted in the current EU specifications.

Constituent particle size for titanium dioxide (E 171) as food additive	Measured by electron microscopy
Median minimal external dimension by number (nm)	More than 100 nm ^(a)

(a) Equivalent to a percentage of constituent particles below 100 nm by number (%) less than 50%

- Based on the proposed **change in the specifications**, revisiting the toxicological database on titanium dioxide (E 171) as a food additive should consequently be conducted in line with the data requirements specified in the **EFSA Guidance on nanotechnology** (EFSA Scientific Committee, 2018).

- The Panel considered the EFSA ANS Panel opinions (2016, 2018) in the light of the current characterisation of the particle size distribution of titanium dioxide (E 171) and concluded that the **conclusions made**, and the uncertainties identified, in the previous EFSA assessments of the food additive E 171 **remain valid**.
- In particular, the characterisation of titanium dioxide (E 171) **does not provide a reason to revise the conclusion on genotoxicity** of titanium dioxide (E 171) previously drawn by the ANS Panel.
- The Panel reiterated the **need for the further research** as recommended in the previous opinions in order to decrease the level of uncertainty and acknowledged that additional studies with characterised E 171 are being carried out by interested business operators

- Dietary Extended One-Generation Reproductive Toxicity: ongoing, to be submitted to EC Mid-2020
- Assessment of titanium dioxide as feed additive **ongoing:** by EFSA FEEDAP Panel;
- Same EOGRTS study has been asked to their applicant: waiting for additional data.



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