Titanium dioxide: Further research is still needed

Update of frequently asked questions to the BfR of 6 May 2020

Titanium dioxide (TiO_2) is authorised as the food additive E 171 and can be used as a white colour pigment in sweets and coatings, e.g. in dragees and chewing gum. Under the nomenclature CI 77891, the substance is contained as a white pigment in cosmetic products such as toothpaste. Titanium dioxide is also used as a UV filter in sunscreen. The majority of titanium dioxide is used in technical applications, however, such as the manufacture of paints, varnish, paper and plastics.

Researchers and the general public are currently discussing the possible health risks which can occur through the uptake of titanium dioxide. The background of this are several new studies, the decision on the classification of titanium dioxide as a hazardous substance on the basis of a recommendation made by the European Chemicals Agency (ECHA) and the ordinance announced in France according to which the marketing of foods containing the food additive E 171 is to be suspended for one year from 2020.

The experts distinguish between oral intake (via food), dermal intake (through the skin) and intake by inhalation (breathed in). Where intake by inhalation is concerned, the European Commission has followed the proposal from the ECHA Risk Assessment Committee (RAC) that titanium dioxide should be classified as a hazardous substance along with the notice “presumably carcinogenic if inhaled” in line with the criteria of the CLP Regulation. The classification proposal was adopted in February 2020 as part of the 14th ATP of the CLP Regulation, and the corresponding Delegated Regulation (EU) No 2020/217 was published in the Official Journal of the European Union. Where oral intake of titanium dioxide as a food additive is concerned, the current status according to the European Food Safety Authority (EFSA) is that the available data gives no indications of a health concern for consumers. An acceptable daily intake (ADI) cannot currently be derived for the food additive, however, as the data base on reproductive toxicity in particular is insufficient and/or inadequate.

EFSA and the BfR will continue to monitor titanium dioxide from a scientific point of view. The data on reproductive toxicity in particular, which is currently being collected in a new study in line with the recommendations of EFSA, will have to be verified. The BfR has compiled some frequently asked questions on the topic of titanium dioxide in food.

What is titanium dioxide and which products contain the substance?

Titanium dioxide (EC 236-675-5, CAS 13463-67-7) is produced in millions of tonnes worldwide. More than 1 million tonnes are produced annually in Europe. Almost 90% of the titanium dioxide is used as white pigment in the manufacture of paints, varnish and printing inks, as well as plastics and paper, and a further 10 % for cosmetics, foods, feeds and pharmaceuticals, where above all the high luminosity and opacity of the white pigment are exploited.

As a food additive with the nomenclature E 171, titanium dioxide can be contained in sweets and coatings among other things, e.g. in dragees and chewing gum. Under the nomenclature CI 77891, the substance is also used in cosmetic products such as toothpaste and sunscreen.

In what forms does titanium dioxide occur?

Titanium dioxide is used as a pigment or as a nanomaterial. Both forms are tasteless, odourless and insoluble.

According to an EU recommendation[1], a nanomaterial exists when the number of particles it contains in unbound state or in an agglomerate/aggregate with a diameter of 1-100 nm (nanometres) is in excess of 50% in at least one spatial dimension. It does not matter here whether this quantity exists in the material intentionally or unintentionally. This recommendation has been taken into account when amending the annexes to the REACH Regulation, which came into force on 01/01/2020 and nanoforms of substances were defined.

Titanium dioxide in nanoform is mainly marketed commercially in two different crystalline forms (anatase or rutile). A material that has often been used as a test material above all in inhalation toxicity studies (designation “P25”), is an 80/20 mixture of anatase and rutile. Commercial nanoforms can also be surface treated. Often a passivating protective coating of the particle surface is applied onto the particles, for example.

Titanium dioxide, specifically produced in nanoform, is used in some consumer products. Above all the high UV filter effect, the transparent properties of nano-forms and advantages in processing are made use of here.

How can titanium dioxide be ingested?

Due to the wide variety of applications, all of the important intake routes have to be looked at within the scope of a health risk assessment of titanium dioxide: intake via the skin (dermal), respiratory tract (by inhalation) or digestive tract (oral). The oral intake may, for example, result from eating food containing the additive E 171. Titanium dioxide is not absorbed via the skin (dermal), when using skincare products. In an opinion on nanoparticles in sunscreen, the BfR therefore assessed uptake via the skin as being safe according to the latest available knowledge when applied to intact, or sunburn-damaged skin. Intake of titanium dioxide nanoparticles by inhalation is possible, such as via the spraying of varnish. This same opinion therefore advised against spray applications, as these can be inhaled (BfR, 2010).

The inhalation of fine particles and especially nanoparticles is generally regarded as critical to health, as studies with animals have shown that they can penetrate deep into the lungs and might cause chronic inflammations. In rats, the inhalation of extremely high titanium dioxide concentrations over a very long period of time (the entire lifespan of the animals) led to the formation of lung tumours. These studies form the basis of the now completed European classification process (see below). The uptake of titanium dioxide via the oral mucosa and/or digestive tract (oral) was taken into consideration in the assessment conducted by EFSA on the use of titanium dioxide as the food additive E 171 and as a component of food contact materials.

The uptake of titanium dioxide as a white pigment in tattoo inks constitutes a special case. Along with “coal black”, titanium dioxide is the most commonly used pigment in tattoo inks. Frequently asked questions specifically about tattoo inks can be found in the BfR’s FAQ of 13 October 2017.

[1] Commission recommendation of 18 October 2011 on the definition of nanomaterials (2011/696/EU). https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32011H0696&from=DE

Which legal regulations apply to the use of titanium dioxide in cosmetic products?

Where use in cosmetic products is concerned, titanium dioxide is included in two positive lists of the EU Cosmetics Regulation (EC) No 1223/2009 (EUCR), firstly in the list of colourants allowed in cosmetic products (Annex IV EUCR) and secondly in the list of authorised UV filters (Annex VI EUCR). Nanoscale and non-nanoscale titanium dioxide is used in UV filters. The transparent appearance of the nanoform is an advantage when applying to the skin. Only specific nanoforms of titanium dioxide are approved at the moment, therefore the current valid version of the Regulation on Cosmetic Products must be taken into account at all times. The EC includes a substance in the positive lists of the EUCR after a safety assessment has been made by the EU Commission's Scientific Committee on Consumer Safety (SCCS). Use of the nanoform of titanium dioxide in sunscreens is not authorised in applications which can lead to exposure of the lungs through inhalation. However, as a result of CLP classification, a new risk assessment of titanium dioxide by the SCCS is necessary pursuant to Article 15 (1) of the Regulation on Cosmetic Products and the European Commission issued a mandate for this purpose on 05 February 2020.

Which legal regulations apply to the use of titanium dioxide in materials without food contact?

No specific legal regulations regarding the use of titanium dioxide exist for materials without food contact, such as textiles and toys. There is a general requirement that the products must be safe and that they may not damage health.

Accordingly, it is prohibited in accordance with Art. 30 of the German Food and Feed Law (LFGB) to produce or treat commodities for others in such a way that they are capable of damaging health due to their composition, in particular through toxicologically effective substances or impurities when put to their intended or foreseeable use. The general safety requirements of the European toy directive 2009/48/EC apply to toys. According to this directive, toys, including the chemical substances they contain, may not endanger the safety of children when put to their intended or foreseeable use under consideration of the behaviour of children.

Thanks to its favourable material properties (chemical and thermal stability, light fastness, high covering properties as white pigment), titanium dioxide is used in various materials which occur in consumer products. It is used as white pigment as well as a texturing component of colour pigments for paints and varnishes. It is also used for décors on paper and porcelain and for the pigmentation of textiles and leather. It finds use in plastics as a coating, dye or stabiliser (UV protection). Other examples of materials containing titanium dioxide are ceramics and glassware. A characteristic feature of these material applications is that the titanium dioxide is bound into a fixed matrix, thus limiting its release.

Which legal regulations apply to the use of titanium dioxide in food contact materials?

Titanium dioxide can be used in food contact materials. The European Framework Regulation (EC) No 1935/2004 "on materials and articles intended to come into contact with food" applies to all food contact materials. It stipulates that materials and articles are to be produced in compliance with good manufacturing practice so that under normal or foreseeable conditions of use they do not transfer their constituents to food in quantities which could

a) endanger human health or

b) bring about an unacceptable change in the composition of the food or

c) bring about an impairment of the organoleptic properties thereof (flavour, taste etc.).

Article 5 of the above Regulation also stipulates the adoption of so-called "specific measures" for certain groups of materials and articles. In the course of a specific measure of this kind, titanium dioxide was authorised for use in food contact materials made of plastic in line with Regulation (EU) No 10/2011. The maximum permissible transfer to food is 60 mg/kg food. The use of titanium dioxide in “nano-structure” is prohibited in this context.

There are no regulations on a European level covering other material groups relevant to titanium dioxide. Within the scope of the "BfR recommendations for food contact materials", titanium dioxide (in nanoform) is listed as a heat stabiliser (max. 3%) in Recommendation XV "Silicone" (e.g. silicone baking moulds) (BfR, 2018). There is no transfer of titanium dioxide from the silicone to the food with a limit of detection of 1.8 µg/kg food. The BfR estimated overall that the aforementioned use of titanium dioxide, from which a maximum daily intake of 0.03 µg/kg body weight (assumed body weight= 60 kg) results, does not pose a risk to health (BfR, 2018).

The BfR assessment was made essentially on the basis of the EFSA assessment (EFSA, 2016; EFSA, 2018). Other data from the literature was also used. The BfR assessed titanium dioxide in the particle size for which the application was made as non-genotoxic after oral intake. This estimation is based in particular on negative *in vivo* tests (Donner et al., 2016; Louro et al., 2014). The substance was also assessed as non-carcinogenic after oral intake. An examination conducted on rats and mice by the National Cancer Institute (NCI) of the U.S. Department of Health and Human Services was regarded as the key study in which, compared to the control group, no differences in the type and number of tumour-like and non-tumour-like tissue damage were detected all the way up to the highest administered dose (50 g/kg feed, equivalent to roughly 2,250 mg/kg body weight/day) (NCI, 1979).

Assessment of titanium dioxide as part of European chemicals assessment

Titanium dioxide is the subject of the European chemicals assessment. One of the processes is the so-called EU-wide harmonised classification, completed in February 2020. The second process is concerned with the evaluation of the substance titanium dioxide within the scope of the European Chemicals Regulation REACH. Both of these regulatory processes were initiated by France. Neither process distinguishes explicitly between conventional titanium dioxide (pigment) and titanium dioxide in nanoform. The scope of the applicable EU Regulations comprises all forms of titanium dioxide.

1) Harmonised classification in line with the CLP Regulation (Regulation (EC) No 1272/2008)

Chemicals with particularly dangerous substance properties (e.g. mutagenic, carcinogenic or damaging to reproduction) are classified throughout the EU in accordance with Regulation (EC) No 1272/2008 on classification, labelling and packaging (“CLP Regulation”). This is a harmonised legal categorisation which is legally binding for manufacturers, importers and users of the substance as such, and which also applies to the substance when used in mixtures if general or, where available, specific concentration limits are exceeded.

A harmonised CLP classification is unbiased as to the application, i.e. it can be made for all chemicals present in the EU market and, if not restricted, it includes all forms of a substance. References to the classification are made in various legal standards and the existence of a harmonised CLP classification, especially the higher hazard categories, sometimes has drastic legal consequences and triggers various risk mitigation measures in other legal areas outside chemicals law (e.g. product law, cosmetics-, toys-, waste law).

Titanium dioxide has now completed the classification process in line with the CLP Regulation. The trigger was a proposal submitted by France in 2015. The Risk

Assessment Committee (RAC) at the European Chemicals Agency (ECHA) concluded in 2017 that titanium dioxide is presumably carcinogenic to humans when inhaled (Category 2, H351 i). A possible health hazard is seen above all in the inhalation of dusts. The process was subject to discussions. The EU Commission completed classification and labelling in October 2019, according to which titanium dioxide [in powder form with at least 1 % of particles with aerodynamic diameter ≤ 10 µm] may be carcinogenic if inhaled. The proposed classification of titanium dioxide was finalised on 18 February 2020 as part of the 14th ATP (Adaption to technical progress) and shall be made mandatory as of 09 September 2021. The corresponding Delegated Regulation (EU) No 2020/217 was published in the Official Journal of the European Union in February 2020[2].

2) Substance evaluation

The substance evaluation in line with the REACH Regulation (EC 1907/2006) serves to verify an initial suspicion regarding the risk a substance poses to health or the environment and to request from the manufacturer or importer of the substance relevant but missing information for the assessment of a risk, and if necessary determine what action has to be taken to minimise it. The initiative for a substance evaluation usually lies with the authorities in each EU Member State.

France started a substance evaluation of titanium dioxide in line with the REACH Regulation in 2018. The process has not yet been completed. From a health point of view, the substance assessment examines whether the available information on properties which indicate mutagenicity, carcinogenicity and toxicity for reproduction is sufficient for a sound risk assessment and safe use or whether more studies will have to be requested. The oral route is not the subject of the substance assessment. Studies conducted in this regard with E 171 as the test material - above all on reproductive and developmental toxicity - are currently being coordinated with the European Food Safety Authority (EFSA). The plan is to take the data in question into consideration when deriving an acceptable daily intake quantity (ADI).

Which legal regulations apply to the use of titanium dioxide as a food additive?

Regulation (EC) No 1333/2008 applies for the use of titanium dioxide as a food additive. In accordance with this, titanium dioxide (E 171) is permitted for use in several food categories applying the *quantum satis*[3] principle. Purity requirements and specifications are laid down in Regulation (EC) No 231/2012. Approval is based on health risk assessments from the Scientific Committee on Food (SCF), which was responsible for this until 2003, the EU Commission, and the European Food Safety Authority (EFSA), which has been responsible since then.

How is the health risk of titanium dioxide as food additive E 171 assessed?

Regarding the **oral intake** of titanium dioxide (E 171) with food, the European Food Safety Authority (EFSA) concluded in 2016 that according to the data available then, there were no indications of a health risk to consumers.

[2] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2020.044.01.0001.01.ENG&toc=OJ:L:2020:044:TOC

[3] According to the terminology of Regulation (EC) No 1333/2008 “Quantum satis” means: “No maximum numerical level is specified and substances shall 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.””

On behalf of the EU Commission, EFSA assessed four new studies in June 2018 (Bettini et al., 2017; Proquin et al., 2017; Guo et al., 2017; Heringa et al., 2016) on the potential toxicity of titanium dioxide as food additive E 171 (EFSA, 2018). There was no subsequent reason for EFSA to revise the assessment of 2016. The BfR regards the EFSA conclusion as reasonable.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) published an opinion on 15 April 2019 on the use of the food additive titanium dioxide (E 171) under consideration of the latest available scientific studies. Thereupon, EFSA drafted its own opinion on the ANSES report on behalf of the EU Commission. EFSA concludes (EFSA, 2019) that the ANSES report published in April 2019 contains no essentially new findings which could cast doubt on the conclusions of the two previous scientific opinions published by EFSA on the use of titanium dioxide as food additive E 171 (EFSA 2016, 2018).

On which studies is the assessment of the European Food Safety Authority (EFSA) based?

The use of titanium dioxide as a food additive (E 171) was assessed by EFSA within the scope of the programme for the reassessment of authorised food additives in accordance with Article 32 of Regulation (EC) No 1333/2008 and Regulation (EU) No 257/2010. EFSA took all available data into account and emphasised in their report of 2016 that the absorption and bioavailability of titanium dioxide are low (maximum 0.1% of the orally ingested quantity) and that the vast majority of an orally ingested quantity is excreted without any change.

EFSA also emphasised that on the basis of the available data on genotoxicity, as well as the data on the absorption, distribution and excretion of titanium dioxide nanoparticles and microparticles, a mutagenic potential of orally ingested titanium dioxide particles (in nano- and micro-form) is unlikely *in vivo*.

With regard to effects on the reproductive system, EFSA pointed out that possibly undesired effects were observed in studies. In these cases, however, titanium dioxide was examined which did not comply with its specifications as food additive E 171. In corresponding studies carried out with the additive E 171, no effects of this kind were observed. As the data basis was limited in this regard, however, EFSA was not able to make a conclusive assessment of its potential for reproductive toxicity. EFSA concluded that although the data situation is not sufficient at the moment to derive an acceptable daily intake (ADI), the available data gives no cause for concern regarding health under consideration of the low oral bioavailability and exposure.

EFSA recommended that more studies be conducted in order to close the gaps that exist with regard to possible effects on the reproductive system and to facilitate the derivation of an acceptable daily intake of the food additive E 171.

What does the Delegated Regulation (EU) No 2020/217 mean for health risk assessments of the use of titanium dioxide as a food additive?

The EU Commission completed classification and labelling in October 2019, according to which titanium dioxide [in powder form with at least 1 % of particles with aerodynamic diameter ≤ 10 µm] may be carcinogenic if inhaled. The corresponding Delegated Regulation (EU) No 2020/217 was published in the Official Journal of the European Union in February 2020.

This decision is based on a scientific opinion from the RAC dated 14 September 2017 which proposed classifying titanium dioxide as carcinogen category 2 by inhalation. In this case, as is listed in the recitals of Regulation (EU) No 2020/217, the titanium dioxide-induced lung carcinogenicity is associated with inhalation of respirable (titanium dioxide) particles,

retention and poor solubility of the particles in the lung This is also known from other particles.

From a toxicological perspective, the conclusion that titanium dioxide particles may be carcinogenic when inhaled is of no relevance for the health risk assessment regarding the use of titanium dioxide as an (orally ingested) food additive.

How does the French government justify the decision to suspend the marketing of foods containing the food additive E 171 for a year from 2020?

The French government issued an ordinance[4] on 17 April 2019 which was promulgated on 25 April. According to this, the marketing of foods containing the food additive titanium dioxide (E 171) is to be suspended in France for a period of one year from 1 January 2020. The French government makes reference in its ordinance to an opinion prepared by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the use of titanium dioxide as food additive E 171 of 12 April 2019, which was published in French on 15 April.

ANSES concluded in April 2019 that there is a lack of scientific data to clarify the uncertainty surrounding the safety to health of the additive E 171. ANSES confirmed its recommendation to generate data on the characterisation of the various physicochemical forms of E 171 and additional toxicological data on the potential health effects of its uptake.

In the recitals of the French ordinance of 17 April 2019, one of the references made is to a study by the Institut National de la Recherche Agronomique (INRA) published on 20 January 2017. This involved a study published by Bettini et al (2017): A team of French researchers administered titanium dioxide marketed as E 171 and containing 44.7% of the particles in the form of nanoparticles to rats per feeding tube over seven days or with their drinking water over 100 days. According to the authors of the study, effects were observed on the immune system along with changes to the intestinal mucosa. Certain inflammatory parameters were also increased and a possibly tumorigenic effect was reported. The statements made in the study are subject to a number of restrictions, however, regarding the transferability of their results to humans and suitability for a risk assessment. Only a very few animals were examined, for instance, many of the reported effects were not significant compared to the control group and the duration of the study was too short to actually assess tumour-forming or tumorigenic effects. Furthermore, there was no dose-effect relationship and it is questionable whether the observations and the manner in which the titanium dioxide was administered are relevant to humans and their intake of titanium dioxide via food. The study authors themselves point out that their findings are merely possible initial indications which require further clarification. Another carcinogenicity study (NCI, 1979) did not produce any indications of tumour-like and non-tumour-like tissue damage, even though significantly higher doses were administered.

The study by Bettini et al. (2017) is one of four assessed by EFSA in June 2018. EFSA also pointed out the weaknesses of this study and concluded that it (as well as the other three studies assessed by EFSA) gave no cause to revise the assessment of 2016 (EFSA, 2018). EFSA's estimation was that the available data gives no cause for concern with regard to health when the low oral bioavailability and exposure are taken into consideration.

What does this ordinance in France mean for Germany?

EFSA concluded in May 2019 (EFSA, 2019) that the ANSES report published in April 2019 contains no essentially new findings which could cast doubt on the conclusions of the two

[4] https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000038410047

scientific opinions published by EFSA on the use of titanium dioxide as food additive E 171 (EFSA 2016, 2018).

Based on a review of the ANSES report, the BfR also came to the conclusion that no reliable scientific arguments can be recognised, which would justify casting doubt on the conclusions of the EFSA opinion on the use of titanium dioxide as a food additive (EFSA, 2016). From the BfR's perspective, research is still required, which is also noted in the EFSA report, in order to improve the data situation regarding titanium dioxide (E 171) as a food additive. The available data does not give cause to think that there are health concerns.

What have the European authorities done up to now?

Food additives must comply with the purity criteria and specifications contained in Regulation (EU) No 231/2012. As particle size distribution has not been listed in this Regulation up to now as a criterion for the specification of titanium dioxide (E 171), EFSA recommended in its report of 2016 on titanium dioxide (E 171) that the specification be amended accordingly. On the initiative of the EU Commission, the EFSA finalised recommendations in June 2019 (EFSA 2019a)[5].

On behalf of the EU Commission EFSA assessed four new studies in June 2018 (Bettini et al., 2017; Proquin et al., 2017; Guo et al., 2017; Heringa et al., 2016) on the potential toxicity of titanium dioxide as food additive E 171 (EFSA, 2018). EFSA concluded that these four studies give no cause to revise the assessment of 2016. The BfR regards the EFSA conclusion as reasonable.

The EFSA reports are usually taken into consideration by risk managers (representatives of the EU Commission and Member States), initially in a committee work group and then if need be, in the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee) in the consultation on any risk management measures which may have to be taken. It is up to Risk Management to decide whether and what measures have to be taken or not. These measures can include alterations to the terms and conditions for use and/or instructing the manufacturers to produce the data in question. Any immediate measures which may be necessary are listed in Articles 53 and 54 of Regulation (EC) No 178/2002. This also applies to the intention of a Member State to take provisional protective measures.

The European Commission requested on 30 January 2017 calling for the studies recommended by EFSA on reproductive toxicity and tests to characterise the food additive to be presented[6]. Further details were published by the EU Commission[7].

The measure of which France gave notice in April 2019 was discussed on EU level in the PAFF Committee (Standing Committee on Plant, Animals, Food and Feed) on 13 May 2019[8].

Further information on the subject from the BfR website:

BfR questions and answers on nanotechnology of 28 August 2012
https://www.bfr.bund.de/cm/349/questions-and-answers-on-nanotechnology.pdf

FAQ on tattoo inks of 13 October 2017
https://www.bfr.bund.de/en/faq_about_tattoo_inks-201880.html

[5] https://www.efsa.europa.eu/de/efsajournal/pub/5760
[6] https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en
[7] https://ec.europa.eu/food/sites/food/files/safety/docs/fs_food-improvement-agents_reeval_call_20170130_e171_data.pdf
[8] https://ec.europa.eu/food/safety/reg_com/toxic_en

Questions and Answers on the Risk Assessment of Cosmetic Products of 3 March 2014
https://www.bfr.bund.de/cm/349/questions-and-answers-on-the-risk-assessment-of-cosmetic-products.pdf

Assessment of potential cancer risk of nanomaterials and nanoparticles released from products, Joint Opinion 005/2011 of the BfR and UBA of 15 April 2010
https://www.bfr.bund.de/cm/349/assessment_of_potential_cancer_risk_of_nanomaterials_and_nanoparticles_released_from_products.pdf

Sunscreen: According to the current state of knowledge zinc oxide as a UV filter is safe, BfR Opinion No. 037/2010 of 18 June 2010
https://www.bfr.bund.de/cm/343/sonnenschutzmittel_zinkoxid_als_uv_filter_ist_nach_derzeitigem_kenntnisstand_gesundheitlich_unbedenklich.pdf

References

ANSES (2019): Additif alimentaire E 171: l'Anses réitère ses recommandations pour la sécurité des consommateurs, Journal officiel de la République Francaise du 25 avril 2019, https://www.anses.fr/fr/content/additif-alimentaire-e171-l%E2%80%99anses-r%C3%A9it%C3%A8re-ses-recommandations-pour-la-s%C3%A9curit%C3%A9-des

ANSES (2019): AVIS de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail relatif aux risques liés à l'ingestion de l'additif alimentaire E 171. Saisine n° 2019-SA-0036. Maisons-Alfort, le 12 avril 2019.
https://www.anses.fr/fr/system/files/ERCA2019SA0036.pdf

Bettini S, Boutet-Robinet E, Cartier C, Coméra C, Gaultier E, Dupuy J, et al. (2017): Food-grade TiO2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. Scientific Reports; 7:40373, doi: 10.1038/srep40373.

BfR (2018): 21. Sitzung der BfR-Kommission für Bedarfsgegenstände - Protokoll vom 7. November 2018. http://m.bfr-meal-studie.de/cm/343/21-sitzung-der-bfr-kommission-fuer-bedarfsgegenstaende.pdf

BfR (2011), Beurteilung eines möglichen Krebsrisikos von Nanomaterialien und von aus Produkten freigesetzten Nanopartikeln, Stellungnahme 005/2011 des BfR und UBA vom 15. April 2010
https://www.bfr.bund.de/cm/343/beurteilung_eines_moeglichen_krebsrisikos_von_nanomaterialien_und_von_aus_produkten_freigesetzten_nanopartikeln.pdf

BfR (2010), Sonnenschutzmittel: Zinkoxid als UV-Filter ist nach derzeitigem Kenntnisstand gesundheitlich unbedenklich, Stellungnahme Nr. 037/2010 des BfR vom 18. Juni 2010
https://www.bfr.bund.de/cm/343/sonnenschutzmittel_zinkoxid_als_uv_filter_ist_nach_derzeitigem_kenntnisstand_gesundheitlich_unbedenklich.pdf

Donner E.M., Myhre A., Brown S.C., Boatman R., and Warheit D.B. (2016): In vivo micronucleus studies with 6 titanium dioxide materials (3 pigment-grade & 3 nanoscale) in orally-exposed rats. Regulatory Toxicology and Pharmacology 74, 64-74. doi: https://doi.org/10.1016/j.yrtph.2015.11.003

ECHA (2017): https://echa.europa.eu/-/titanium-dioxide-proposed-to-be-classified-as-suspected-of-causing-cancer-when-inhaled

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food) (2016): Scientific Opinion on the re-evaluation of titanium dioxide (E 171) as a food additive. EFSA Journal;14(9):4545, 83 pp. doi:10.2903/j.efsa.2016.4545, https://www.efsa.europa.eu/de/efsajournal/pub/4545

EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food) (2018): Evaluation of four new studies on the potential toxicity of titanium dioxide used as a food additive (E 171). EFSA Journal; 16(7):5366, doi: 10.2903/j.efsa.2018.5366 https://www.efsa.europa.eu/en/efsajournal/pub/5366

EFSA (2019): EFSA statement on the review on the risks related to the exposure to the food additive titanium dioxide (E 171) performed by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). EFSA Journal 2019; 17 (6): 5714, 11 pp. doi:10.2903/j.efsa.2019.5714, https://www.efsa.europa.eu/en/efsajournal/pub/5714

EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings) (2019a) Scientific opinion on the proposed amendment of the EU specifications for titanium dioxide (E 171) with respect to the inclusion of additional parameters related to its particle size distribution. EFSA Journal 2019;17(7):5760, 23 pp. https://www.efsa.europa.eu/de/efsajournal/pub/5760

EU-Kommission (2020): 14. ATP (Delegierte Verordnung (EU) 2020/217) zur CLP-Verordnung ((EG)1272/2008). Amtsblatt der Europäischen Union 2020, L44/14. https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32020R0217&from=DE

EU-Kommission (2020): Scientific Committee on Consumer Safety. Request for a scientific opinion on Titanium dioxide used in cosmetic products. https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs2016_q_043.pdf

EU-Kommission (2018): Verordnung (EU) 2018/1881 der Kommission. Amtsblatt der Europäischen Union 2018, L 308/1. https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32018R1881&from=EN

EU-Kommission (2011): Empfehlung der Kommission vom 18. Oktober 2011 zur Definition von Nanomaterialien (2011/696/EU). https://eur-lex.europa.eu/legal-content/DE/TXT/PDF/?uri=CELEX:32011H0696&from=DE

Guo Z, Martucci N, Moreno-Olivas F, Tako E and Mahler G (2017): Titanium dioxide nanoparticle ingestion alters nutrient absorption in an in vitro model of the small intestine. NanoImpact, 5, 70-82, doi: 10.1016/j.impact.2017.01.002.

Heringa MB, Geraets L, vanEijkeren JCH, Vandebriel RJ, deJong W and Oomen AG (2016): Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations. Nanotoxicology, 10, doi: 10.1080/17435390.2016.1238113

IARC (International Agency for Research on Cancer) (2010): “Carbon black, titanium dioxide, and talc,” in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 93, International Agency for Research France,

https://monographs.iarc.fr/wp-content/uploads/2018/06/mono93.pdf

Kreyling WG, Holzwarth U, Haberl N, et al. (2017): Quantitative biokinetics of titanium dioxide nanoparticles after intratracheal instillation in rats: Part 3. Nanotoxicology, Published online 03 April 2017, http://dx.doi.org/10.1080/17435390.2017.1306894

Louro H., Tavares A., Vital N., Costa P.M., Alverca E., Zwart E., Jong W.H., Fessard V., Lavinha J., and Silva M.J. (2014): Integrated approach to the in vivo genotoxic effects of a titanium dioxide nanomaterial using LacZ plasmid-based transgenic mice. Environmental and Molecular Mutagenesis 55 (6), 500-509. doi:10.1002/em.21864

Ministère de l'Economie et des Finances (2019): Arrêté du 17 avril 2019 portant sur la suspension de la mise en marché des denrées contenant l'additif E 171 (dioxyde de titane - TiO2), https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000038410047

National Institute for Occupational Safety and Health (2011): Current Intelligence Bulletin 63: Occupational Exposure to Titanium Dioxide, April, https://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf

NCI (1979): BIOASSAY OF TITANIUM DIOXIDE FOR POSSIBLE CARCINOGENICITY. National Cancer Institute. Carcinogenesis. Technical Report Series 97 (NCI-CG-TR-97). https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr097.pdf

Proquin H, Rodriguez-Ibarra C, Moonen CG, Urrutia-Ortega IM, Briede JJ, de Kok TM, van Loveren H and Chirino Y (2017): Titanium dioxide food additive (E 171) induces ROS formation and genotoxicity: contribution of micro and nano-sized fractions. Mutagenesis, 32, 139-149, doi:10.1093/mutage/gew051

Ruiz PA, Morón B, Becker HM, Lang S, Atrott K, Spalinger MR, et al. (2016): Titanium dioxide nanoparticles exacerbate DSS-induced colitis: Role of the NLRP3 inflammasome. Gut. doi:10.1136/gutjnl-2015-310297

Weir, A., Westerhoff, P., Fabricius, L., Hristovski, K. & von Goetz, N. (2012): Titanium Dioxide Nanoparticles in Food and Personal Care Products. Environ Sci Technol 46, 2242-2250, doi:10.1021/es204168d

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the German federal government and German federal states ("Laender") on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

This text version is a translation of the original German text which is the only legally binding version.