Titanium dioxide – there is still a need for research

Frequently asked questions to the BfR of 22 May 2019

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. The substance is also contained in cosmetic products such as toothpaste or as nanoparticles in sunscreen under the name CI 77891. 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 still pending 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 recently pronounced 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 (via food), dermal (through the skin) and inhalative (breathed in) intake. Where inhalative intake is concerned, the ECHA Risk Assessment Committee (RAC) has proposed that titanium dioxide be classified as a hazardous substance along with the notice “presumably carcinogenic if inhaled” in line with the criteria of the CLP regulation. 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.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) concluded in April 2019 that there is a lack of scientific data to dispel the uncertainties relating to the health safety of the additive E 171. In its recommendations, ANSES emphasised the need for data to characterise the various physicochemical forms of E 171 and additional toxicological data on the possible effects of its uptake. EFSA concluded in May 2019 that the ANSES opinion does not contain any essentially new findings which would cast doubt on EFSA’s current assessment of the use of titanium dioxide (E 171) as a food additive (EFSA, 2019).

The French ministries of the environment and economics announced in April 2019 that foods containing the additive E 171 may not be brought into circulation in France from 2020 for a period of one year.

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?
The chemical titanium dioxide (EC 236-675-5, CAS 13463-67-7) is produced all over the world on a scale of millions of tonnes. Europe alone produces over a million tonnes every year. 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 designation E 171, titanium dioxide can be contained in sweets and coatings among other things, e.g. in dragees and chewing gum. Under the designation CI 77891, the substance is also used in cosmetic products such as toothpaste and sunscreen.

Titanium dioxide is also manufactured specifically in nano-form for use in several consumer products. Above all the high UV filter effect, the transparent properties of nano-forms and advantages in processing are made use of here. A certain percentage of nanoparticles is usually contained for production reasons apparently.

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.

What exactly a nanomaterial is has not yet been defined in European substance law. 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. Titanium dioxide in nano-form 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 nano-forms can also be surface treated. Often a passivating protective coating of the particle surface is applied onto the particles, for example.

How can titanium dioxide be ingested?
Titanium dioxide can be ingested via the digestive tract (orally), skin (dermally) or respiratory tract (inhalatively). Oral intake results from eating foods containing the additive E 171. Dermal intake comes from cosmetic or tooth care products containing titanium dioxide, while inhalative intake of titanium dioxide nanoparticles is possible from the spraying of sunscreens or paints, for example.

Due to the wide variety of applications, all of the important intake routes have to be looked at within the scope of a health assessment of titanium dioxide: intake via the skin, respiratory tract or digestive tract. In an opinion on nanoparticles in sunscreen, the BfR assessed uptake via the skin as being safe according to the latest available knowledge when applied to intact,

[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

or sunburn-damaged skin. This same opinion advised against spray applications, however, 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 European classification process which is currently running (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.

In which legal process is titanium dioxide being assessed?

Titanium dioxide is currently the subject of two processes of European chemicals assessment. The purpose of the one process is the so-called EU-wide harmonised classification. The second process is concerned with the assessment 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 nano-form. The scope of the applicable EU regulations comprises all forms of titanium dioxide.

1) Harmonised classification in line with the CLP regulation (Reg. (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 reduction measures in other legal areas outside chemicals law (e.g. product law, cosmetics-, toys-, waste law).

Titanium dioxide is currently undergoing the classification procedure in line with the CLP regulation. A proposal to this effect was 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, H350 i). A possible health hazard is seen above all in the inhalation of dusts. The process is currently a topic of intense discussion regarding the drafting of a possible entry in the wording of the relevant laws in a manner that does justice to the protection goal of REACH regulation but has not yet been completed (as of 1 May 2019).

2) Substance assessment

The substance assessment 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 assessment usually lies with the authorities in each EU member state.

France started a substance assessment 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 to the use of titanium dioxide as a food additive. According to this regulation, the use of titanium dioxide (E 171) is authorised in several food categories applying the *quantum satis* principle[2] as the maximum quantity. The purity requirements and specifications are regulated by Regulation (EU) No. 231/2012. Authorisation is based on the health assessments made by the EU Commission's Scientific Committee on Food (SCF), which was responsible until 2003, and the European Food Safety Authority (EFSA) which has held responsibility ever since (see FAQ on the health assessment below).

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) Nr. 1223/2009 (EUCR), firstly in the list of colorants allowed in cosmetic products (Annex IV EUCR) and secondly in the list of authorised UV filters (Annex VI EUCR). The nano-form of titanium dioxide is used in UV filters because the transparent appearance of the nano-form is of advantage when applying to the skin. A substance is included 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 nano-form of titanium dioxide in sunscreens is not authorised in applications which can lead to exposure of the lungs through inhalation (i.e. in certain sprays).

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

[2] According to the definitions contained in Regulation (EC) No. 1333/2008, "quantum satis" means that: "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."

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 contaminants, 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 decors 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 so-called 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 a deterioration of the organoleptic characteristics 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 nano-form) 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 afore-mentioned 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).

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, EFSA concluded in 2016 that according to the data available then, there were no indications of a health risk to consumers. 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 considers the EFSA conclusion to be 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 reports 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.

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 ordinance on 17 April 2019[3] which was pronounced on 25 April according to which 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) in which 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-response 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 (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.

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

What does this ordinance mean for Germany? Could the level of available knowledge make measures similar to those taken in France necessary in Germany too?
After making a short-term review of the ANSES report, which focused on aspects which appear to be essential, no reliable scientific arguments can be recognised, in the view of the BfR, which would justify casting doubt on the conclusions of the EFSA opinion on the use of titanium dioxide as a food additive (EFSA, 2016). As the authorisation process for food additives takes place on EU level, a detailed review of the ANSES report, including a review of the publications quoted in it, would be the responsibility of the EU Commission, which can give EFSA the mandate to do so.

What have the 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. At the behest of the EU Commission, EFSA established a work group in December 2018 in which appropriate suggestions are to be drawn up[4].

In June 2018 EFSA assessed four new studies on the potential toxicity of titanium dioxide as food additive E 171 (Bettini et al. 2017; Proquin et al. 2017; Guo et al. 2017; Heringa et al. 2016) at the request of the EU Commission (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 published a call for data[5] on 30 January 2017 calling for the studies recommended by EFSA on reproductive toxicity and tests to characterise the food additive to be presented. The result of this call for data with regard to the interested business operators[6], the data to be provided and the deadlines[7] by which the data is to be presented were also published by the EU Commission. Accordingly, the presentation of data on particle size distribution was announced for June 2018, on reproductive toxicity by August 2019, on

[4] The minutes of the meetings can be accessed at https://www.efsa.europa.eu/en/food-ingredients-and-packaging/working-groups
[5] https://ec.europa.eu/food/safety/food_improvement_agents/additives/re-evaluation_en
[6] https://ec.europa.eu/food/sites/food/files/safety/docs/fs_food-improvement-agents_reeval_call_20170130_e171_data.pdf
[7] https://ec.europa.eu/food/sites/food/files/safety/docs/fs_food-improvement-agents_reeval_call_20170130_e171_outcome-2.pdf

contamination through heavy metals by October 2017 and on aluminium levels in titanium dioxide by September 2017.

The measure of which France gave notice in April 2019 was discussed on EU level in the PAFF Committee[8] on 13 May 2019.

More information on the topic at 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/cm/349/faqs-on-tattoo-inks.pdf

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/349/sunscreen_according_to_the_current_state_of_knowledge_zinc_oxide_as_uv_filter_is_safe.pdf

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[8] https://ec.europa.eu/food/safety/reg_com/toxic_en

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