German Federal Institute for Risk Assessment

Communication 028/2025

1 August 2025

ECJ upholds overturning of titanium dioxide's classification as "probably carcinogenic when inhaled"

The European Court of Justice (ECJ) has upheld the decision of the Court of Justice of the European Union (CJEU). Therefore, the classification of titanium dioxide in powder form as "probably carcinogenic when inhaled" remains invalid.

In 2020, the European Commission classified titanium dioxide in powder form as "probably carcinogenic when inhaled." The substance was then included in the CLP Regulation (EC) No. 1271/2008, which regulates the classification, labelling, and packaging of chemicals throughout the EU. This classification applied exclusively to particles that can enter the lungs when inhaled.

The Court of Justice of the European Union (CJEU) annulled this decision in 2022 due to methodological shortcomings in the underlying studies and violations of the CLP Regulation. An appeal was then lodged against this ruling. In response to inquiries, the German Federal Institute for Risk Assessment (BfR) has compiled the following information on titanium dioxide.

Titanium dioxide (TiO_2) is produced worldwide in millions of tonnes. Most of the TiO_2 produced is used in technical applications such as for the manufacture of paints, coatings, paper, and plastics. Under the name CI 77891, the substance is used as a white pigment in cosmetic products such as toothpaste. TiO_2 is also used as a filter in sunscreens to protect against ultraviolet radiation. Until 2022, TiO_2 was also approved as food additive E 171.

The current state of research on TiO_2 with regard to **genotoxicity** (damage to genetic material) and **carcinogenicity** (cancer-causing potential) is complex and inconclusive.

Genotoxicity

In its 2021 risk assessment, the European Food Safety Authority (EFSA) concluded that genotoxic potential of TiO_2 cannot be ruled out. The remaining uncertainty led to TiO_2 being

withdrawn as food additive E 171 throughout the EU.. Since 8 August 2022, foods containing E 171 may no longer be placed on the market.

Carcinogenicity

In 2006, the International Agency for Research on Cancer (IARC) classified TiO_2 as "possibly carcinogenic to humans" (Category 2B). This classification is based on animal studies in which lung cancer was detected after inhalation of high doses of respirable TiO_2 particles (< 10 µm).

Under the CLP Regulation (EC) No. 1271/2008, which regulates the classification, labelling, and packaging of chemicals throughout the EU, the EU Commission harmonised the classification of TiO_2 in powder form in 2020 as "probably carcinogenic when inhaled" (Category 2, H351i). A harmonised classification is a legally binding classification of a substance, which is then included in Annex VI of the CLP Regulation. However, the harmonised classification for carcinogenic effects referred exclusively to the inhalation of respirable particles.

This decision was overturned by the Court of Justice of the European Union (CJEU) in 2022 as the underlying scientific studies had methodological weaknesses (e.g. insufficient consideration of lung overload and particle properties). An appeal was then filed against this ruling.

In this context, it is important to distinguish between risk assessment and an assessment of hazard potential. A risk assessment always considers harmful effects on human health (potential hazards) along with an exposure assessment (including investigation of exposure routes, amounts, duration, etc.). For classification in accordance with the CLP Regulation, only the hazard potential is considered. Classification is based on hazard classes (i.e. what harmful effects are possible) and hazard categories (severity of the possible damage). Assessments according to the CLP Regulation are not risk assessments and do not allow any general conclusions to be drawn regarding an actual health risk.

Study situation

The study situation for TiO_2 is unclear and ambiguous for several reasons. Existing studies differ in methodology. Some studies are based on research carried out through animal testing (*in vivo*), while others describe examinations of cells cultivated in the laboratory (*in vitro*). The TiO_2 particles examined also differ in various particle properties, such as particle size, crystal structure, and/or surface coating. Furthermore, there are differences in the studies with regard to the exposure routes considered (oral, dermal, inhalation), the specific doses administered, and the form of administration.

Particle-specific characteristics must not only be taken into account in the subsequent evaluation of the studies, but should already be considered in the study design and implementation. This is not always done to a sufficient extent. The evaluation of studies involving particles is therefore always more time-consuming and complicated/complex than comparable studies involving soluble substances.

In 2022, the CJEU criticised methodological uncertainties in the studies that served as the basis for the European Commission's legal classification. For example, the ruling objected to the notion that TiO_2 has the intrinsic property of causing cancer. TiO_2 only has carcinogenic potential under very specific conditions (e.g. the presence of respirable particles in large quantities combined with simultaneous overload of the lung's clearance mechanism). The court emphasises the need to clearly distinguish between mechanisms of action in humans and context-dependent effects (e.g. particle toxicity),.

The German Federal Institute for Risk Assessment (BfR) has already compiled information on the study situation in its questions and answers on titanium dioxide.

Particle size

The size of TiO_2 particles is a decisive factor. In the context of the harmonised classification according to the CLP Regulation, the size of the particles determines whether they are inhalable and, if so, how deep the particles can penetrate into the lungs. The aerodynamic diameter is relevant in this context. A distinction is made between:

a) Larger particles (> 10 µm):

Particles of this size are not respirable and are considered less problematic as they are retained in the upper respiratory tract and subsequently coughed up.

b) Respirable particles (≤ 10 µm):

Particles with an aerodynamic diameter of ≤ 10 µm can be inhaled and cause inflammation or fibrosis in the lungs.

c) Particles smaller than 100 nm (nanoparticles):

These particles can penetrate even deeper into the lungs (into the alveolar region) where they can cause inflammation or mechanical damage.

The harmonised classification of TiO_2 targeted particle sizes that are respirable and have been shown to cause lung cancer in animal studies.

Risks depending on the route of exposure

The potential risks of TiO_2 vary greatly depending on the route of exposure. This information has already been compiled in the BfR's FAQ on titanium dioxide.

Inhalation

The highest risk of potential intake is through inhalation. This applies to respirable particles (≤ 10 µm) and nanoparticles. Animal studies have shown pneumonia, fibrosis and, when very high doses were administered over a long period of time, lung cancer. The postulated mechanism of action involves overloading the lungs with too many particles and overwhelming the associated lung's clearance mechanisms. See also the Guidelines for the

Application of the Harmonised Titanium Dioxide Classification (in German) by the German Federal Institute for Occupational Safety and Health (BAuA).

Oral intake

In its 2021 assessment, EFSA stated that smaller particles in particular can be absorbed through the gastrointestinal tract and thereby become systemically available. These particles do not dissolve, meaning they are biopersistent. Furthermore, a genotoxic effect could not be ruled out.

Skin contact

TiO_2 is not absorbed through intact skin, neither in micro nor in nano form. Studies show no systemic effects with dermal application (e.g. in sunscreens). There is therefore no health risk.

Sunscreens

Based on the available evidence, nano-TiO_2 used as a UV filter in concentrations of up to 25 percent in sunscreens is not expected to cause any adverse health effects. Studies show that nano-TiO_2 in the forms used in cosmetic products cannot enter the human bloodstream.

The use of TiO_2 in sunscreens has been evaluated by the Scientific Committee on Consumer Safety (SCCS) of the European Commission and is regulated in the EU Cosmetics Regulation EC (No.) 1223/2009 (Annex VI, reference numbers 27 and 27a). According to this, TiO_2 is not generally prohibited in sprays, but only in those that, due to the (small) particle size, can lead to exposure of the user's lungs through inhalation. There are also sprays (e.g. pump sprays) in which the particles are so large that they do not reach the deeper lungs and therefore no inhalation exposure occurs.

Toothpaste

The use of TiO_2 in toothpastes is currently being reassessed by the SCCS. This current assessment has not yet been completed. The German Federal Institute for Risk Assessment (BfR) will refrain from commenting on ongoing SCCS assessments. However, a statement by the SCCS published in 2024 indicates that the TiO_2 variants intended for use in cosmetic products differ from E 171, the material considered in the EFSA opinion.

Medical drugs

TiO_2 (E 171) is added to medical drugs as a colourant. This use is still permitted in the EU in accordance with Directive 2009/35/EC on substances that may be added to medical drugs for colouring purposes. Through a footnote, a corresponding cross-reference has been added to the entry for TiO_2 (E 171) in Regulation (EC) No. 1333/2008 on food additives in Annex B, Part 2 (contains a list of all additives).

For further questions regarding medical drugs, please refer to the German Federal Institute for Drugs and Medical Devices (BfArM).

Further information on the BfR website on titanium dioxide

Titanium dioxide – are there health risks?
https://www.bfr.bund.de/en/service/frequently-asked-questions/topic/titanium-dioxide-are-there-health-risks/

Further information from other institutions on titanium dioxide

2022 Ruling of the Court of Justice of the European Union (CJEU)
https://curia.europa.eu/juris/document/document.jsf;jsessionid=C5F4CB0B8CB60255A9536543BE199B5A?text=&docid=295077&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=36748
2022 Judgment of the Court of Justice of the European Union (CJEU) from 2022
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:62020TJ0279

About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent public health institute within the portfolio of the German Federal Ministry of Agriculture, Food and Regional Identity (BMLEH). The BfR advises the Federal Government and the States ('Laender') on questions related to food, feed, chemical and product safety. The BfR conducts independent 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.

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Responsible according to the German Press Law: Dr Suzan Fiack

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