Additional Evaluations - Toxicity of Titanium Dioxide as a Food Additive

In this guide

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This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

33. Before expanding on the 2021 EFSA evaluation of Titanium dioxide following the 2019 recommendation, additional evaluations by other scientific bodies that were published prior to 2021 are discussed in the section below.

ANSES and ECHA (European Chemicals Agency)

34. Following a report by the French Authorities in 2016, and a proposal for

evaluation of titanium dioxide the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) concluded in June 2017 that titanium dioxide met the criteria to be classified as a substance suspected of causing cancer (category 2) if inhaled.

35. The main mechanism to explain the effects induced by titanium dioxide, in common with effects seen with other substances, was inflammation and an indirect genotoxic effect through production of reactive oxygen species (ROS) arising from the biopersistence and insolubility of all forms of titanium dioxide particles. However, a direct interaction with DNA could not be excluded, since titanium dioxide was found in the cell nucleus in various in vitro and in vivo studies.

36. This was in line with the International Agency for Research on Cancer (IARC) evaluation which concluded that “titanium dioxide is possible carcinogenic to humans (Group 2B) based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies. ” This was with relation to exposure via inhalation. However, in the same report by the French Authorities, ANSES concluded that there was no carcinogenic concern after oral or dermal administration.

Dutch Office for Risk Assessment

37. In 2018, the Dutch Office for Risk Assessment and Research held a workshop on the “potential health effects of the food additive titanium dioxide (E171)”, the results of which were published in 2019 , where overall the need for further studies to further investigate the effects of titanium dioxide exposure-particularly for the endpoints of colon tumours and immunotoxicology based on the data gaps and study limitations of the available database at the time was highlighted. Furthermore the need to better characterise the composition of E171 was noted.

38. In 2020, a review was published that summarised the outcomes of this workshop and additionally aimed to identify and evaluate recent toxicological studies on food-grade titanium dioxide and nano-sized titanium dioxide in ex-vivo, in-vitro, and in-vivo experiments along the gastrointestinal route, and to postulate an Adverse Outcome Pathway (AOP) following ingestion.

39. Adverse effects were identified including the generation of ROS, alterations of the gut microbiota, persistent inflammation, and other effects on

the immune system. It was noted that findings were inconsistent between the different species and independent research groups.

40. With regards to the animal studies which reported positive effects with respect to precancerous lesions/tumour formation, it was noted that those were mainly used as research models and a proper investigation of a dose-response relationship was not performed. Based on the available information, it was not possible to carry out a risk assessment.

41. When considering the mode of action, it was postulated that it was closely related to the ability of titanium dioxide to induce ROS formation and promote inflammation. The potential key events were considered to be persistent inflammation and ROS generation that can result in oxidative stress as well as persistent epithelial cell injury and potentially lead to DNA damage and exert a tumour-promoting effect of E171 seen in some of the studies.

42. Finally, it was noted that it is generally assumed that the round and spherical crystal forms of TiO_2 contribute to a lower extent to the induction of adverse effects, when ingested and similarly that titanium dioxide nanoparticles are suspected to induce more adverse effects than other particle sizes. However, a study by Proquin et al.(2017) was also mentioned, that demonstrated that a mixture of nano- and micro-sized TiO_2 particles, as they are present in E171, induce more adverse effects than the single fractions alone.

43. The authors further expanded on possible interactions of E171 with its direct environment as well as other factors that could potentially affect agglomeration for example and discussed how these could directly affect the properties of titanium dioxide.

44. Therefore, they considered that “it is important to carefully examine and analyze the physicochemical characteristics of TiO_2 particles in its vehicle, as well as in its surrounding matrix as their final milieu, to guarantee a profound assessment of potential adverse health effects of E171 and to adequately compare different studies in the process of risk assessment.” (Bischoff et al.,2020).

Scientific Committee on Consumer Safety (SCCS)

45. The EU Scientific Committee on Consumer Safety (SCCS) assessed titanium dioxide used in cosmetic products that lead to exposure by inhalation.

With regards to mutagenicity and genotoxicity, the SCCS noted that in the 2010 evaluation, IARC concluded that that most of the in vitro genotoxicity studies with titanium dioxide exposure were negative despite the high rate of false positives and that the EFSA Panel in 2016 considered that the positive genotoxicity results may have been due to experimental conditions associated with the induction of oxidative stress.

46. The SCCS also noted that studies showing a positive association between the so-called group of Poorly Soluble Low Toxicity (PSLT) particles exposures and genotoxicity are generally consistent with the mechanism that sub-toxic concentrations of PSLT particles can cause inflammation and oxidative stress, which may lead to mutations.

47. Oxidative stress is considered to be the underlying mechanism of the proliferation and genotoxic responses to PSLT particles including titanium dioxide and thus there is a large body of evidence that titanium dioxide has no direct genotoxic potential.

48. The SCCS was of the opinion that “The genotoxic effects of titanium dioxide most probably manifest through an indirect mechanism (oxidative stress), or secondary mechanisms (e.g. oxidative stress and inflammation caused by immune cells).

49. The SCCS therefore considered it plausible that there is a practical threshold for this mode of action and therefore a risk assessment could be carried out for its use in cosmetic products.” They concluded that when used in cosmetic products titanium dioxide does not pose a genotoxic risk. (SCCS, 2020). Genotoxicity is not considered further in this paper.