

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and materials in Contact with Food on a request from the Commission related to

the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form

Question N° EFSA-Q-2004-103

Adopted on 7 December 2004

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids And Materials In Contact With Food has been asked to evaluate the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form.

Titanium dioxide is an approved food colour with an ADI “not specified” by JECFA. The 1969 JECFA assessment based this on the lack of significant absorption and tissue storage in several species including humans. In the European Union Titanium Dioxide (E171) is listed in Annex I of Directive 94/36/EEC as a permitted colour in foodstuffs. Titanium dioxide can be manufactured to form two crystal structures, anatase and rutile. The current specification for titanium dioxide in Directive 94/36 only permits the anatase form. The JECFA specification for titanium dioxide allows both forms.

The Panel considered that the rutile and anatase forms of titanium dioxide were similar chemically but differed in their crystalline structure and light reflectance. The Panel agreed that a new bioavailability study showed that bioavailability of these forms was essentially the same and that therefore the toxicological database would be applicable to either form. The Panel noted that although estimated exposures were provided for the petitioner’s proposed uses of the platelet form of rutile titanium dioxide, the platelet form of rutile titanium dioxide could be used to replace anatase titanium dioxide in any of its current applications.

KEYWORDS

Titanium dioxide, E171, food colours, CAS 13463-67-7

BACKGROUND

Titanium dioxide is an approved food colour with an ADI “not specified” by JECFA. The 1969 JECFA assessment based this on, the lack of significant absorption and tissue storage in several species including humans. The SCF in its first report (1975) did not establish an ADI for titanium dioxide but accepted its use for sugar confectionery “without the need for further investigations”, the SCF subsequently extended this to food use in general in its fourth report (1977).

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Titanium dioxide can be manufactured to form two crystal structures, anatase and rutile. The rutile form can be formed into platelets on a mica (potassium aluminium silicate) template which is removed by extractive dissolution in acid and then alkali. The layer thickness of the rutile form of titanium dioxide determines the colour of the product.

Directive 94/36/EC on colours for use in foodstuffs authorises the use of Titanium dioxide (E 171) as a permitted colour in foodstuffs. Directive 95/45/EC laying down specific purity criteria for food colours specifies that “*titanium dioxide consists essentially of pure anatase titanium dioxide which may be coated with small amounts of alumina and/or silica to improve technological properties of the product*”. The JECFA specification for titanium dioxide would allow both forms.

TERMS OF REFERENCE

The Commission asks EFSA to evaluate the safety in use of rutile titanium dioxide as an alternative to the presently permitted anatase form.

ASSESSMENT

Chemistry

Titanium dioxide TiO_2 , CAS: 13463-67-7, Molecular weight: 79.9, C.I. (1975) No.77891, C.I. Pigment White 6

Specifications

The current EU specification for titanium dioxide for food uses is in Directive 95/45/EC. A proposed specification including the rutile form of titanium dioxide is at annex 1 to this Opinion.

Manufacturing process

Titanium dioxide can be manufactured to form either the anatase crystal structure or the rutile crystal structure. The anatase grades of pigmentary titanium dioxide can only be made by the sulphate process which creates a large amount of sulphuric acid as a by-product. The rutile grades of titanium dioxide are typically made by the chloride process.

Certain rutile grades of titanium dioxide are produced using mica (also known as potassium aluminum silicate) as a template to form the basic platelet structure. The surface of the mica is coated with titanium dioxide using a specialised patented process.

Rutile titanium dioxide, platelet form is manufactured by subjecting titanium dioxide (rutile) coated mica nacreous pigment to an extractive dissolution in acid followed by an extractive dissolution in alkali. All of the mica is removed during this process and the resulting product is a platelet form of rutile titanium dioxide. This product cannot be obtained from anatase titanium dioxide as a starting material. The specific properties of the pigment are determined

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by controlling the thickness of the titanium dioxide layer and the coating process used to coat the mica substrate. The layer thickness of the rutile titanium dioxide coated on the mica determines the interference colour of the final product. The resulting platelet titanium dioxide obtained via this process contains low levels of impurities comparable to other standard pigment grades of titanium dioxide typically used in the food industry.

Existing authorisations and evaluations

Titanium dioxide (E 171, INS 171) is approved for use in food by the European Union, by the United States FDA and by the Codex Alimentarius of the FAO/WHO. The Joint WHO/FAO Expert Committee of Food Additives (JECFA) evaluated titanium dioxide and allocated an Acceptable Daily Intake not specified (JECFA 1969). In addition to the safety evaluation, JECFA established a set of purity criteria for titanium dioxide which do not differentiate between the anatase and rutile forms of titanium dioxide. In the European Union, titanium dioxide (E171) is included in the list of approved colouring agents in Directive 94/36/EC. The purity criteria, however, mention explicitly that titanium dioxide essentially consists of the pure anatase form which may be coated with small amounts of alumina and/or silica to improve the technological properties of this product.

Rutile titanium dioxide, platelet form is currently used in aqueous film coating systems for commercial confectionery products in the United States. Rutile titanium dioxide, platelet form is permitted for food and drug use in the United States (under 21 CFR § 73.575). Rutile titanium dioxide, platelet form is being evaluated for the use in cookies, pretzels, baked goods, salted snacks, and confectionery products in the United States.

Case of need and proposed uses

According to the petitioner rutile titanium dioxide, platelet form will be used in film coatings for food supplement tablets and foodstuffs. The petitioner also envisages that it will be used in medicinal product tablets.

Exposure

Estimates of the dietary intake of the platelet form of rutile titanium dioxide based on the quantity expected to be added to foods (including food supplements and confectionery) and medicinal products were provided by the petitioner and are described below.

Use-levels for the platelet form of rutile titanium dioxide as a colour additive in aqueous film coatings for tablet applications assumed that application results in 3.0% weight gain per tablet and a rutile titanium dioxide content of 12.5%. Maximum estimates for the use levels were derived by selecting a maximum daily intake of tablets of the following specified sizes; 20 200mg tablets per day for a medicinal product and 10 1000mg tablets per day for a food supplement. This results in a potential daily exposure of 15 mg of rutile titanium dioxide from medicinal products, which equates to approximately 0.25 mg/kg body weight/day for a 60kg individual and a potential daily exposure of 37.5 mg of rutile titanium dioxide from food supplements, which equates to approximately 0.625 mg/kg body weight/day.

The estimates for exposure to rutile titanium dioxide, platelet form from the use of foodstuffs (confectionery and food supplement tablets) and medicinal product tablets containing the

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platelet form of rutile titanium dioxide are presented in Table 1. The estimates are likely a gross over-estimate of potential total exposures to the platelet form of rutile titanium dioxide since it was assumed that all confectionery products, food supplement tablets and medicinal products contained the platelet form of rutile titanium dioxide at the maximum specified level of use. Therefore, addition of the consumption from the uses in confectionery, food supplement tablets, medicinal products is considered by the petitioner to represent a “worst case” scenario.

Use-levels for the platelet form of rutile titanium dioxide as a colour additive for a food or confectionery product assumed that application results in 0.34% weight gain of which the rutile titanium dioxide content is 20.0%. Using these assumptions and data from the US National Confectioners Association on the per capita confectionery consumption (chocolate and non-chocolate uses) in various Member States in the European Union, daily consumption from confectionery in these countries of the platelet form of rutile titanium dioxide would range from 0.071 to 0.495 mg/kg body weight/day. These are probably over estimates since they assume that all the confectionery is coated with a coating containing the platelet form of rutile titanium dioxide at the maximum specified level of use.

TOXICOLOGICAL DATA

JECFA evaluated the safety of titanium dioxide including studies on absorption, distribution, metabolism, excretion, acute, short-term and long-term toxicity. JECFA concluded that: “Titanium dioxide is a very insoluble compound. The studies in several species, including man, show neither significant absorption nor tissue storage following ingestion of titanium dioxide. Studies on soluble titanium compound have therefore not been reviewed. It is useful to note that following absorption of small amounts of titanium ions no toxic effects were observed. Establishment of an acceptable daily intake for man is considered unnecessary.” (JECFA 1969).

In addition to the toxicological database evaluated by JECFA (JECFA 1969), additional bioavailability (Colorcon, 2003), chronic toxicity and carcinogenicity studies (NCI, 1979; Bernard *et al.*, 1990) have more recently been carried out on titanium dioxide and have been evaluated by the Panel, as follows.

Absorption, distribution, metabolism and excretion

A new bioavailability study (Colorcon, 2003) was conducted in the rat to evaluate the absorption, distribution and excretion (ADE) of the following four grades of titanium dioxide as described by the petitioner:

1. rutile titanium dioxide (thick platelet),
2. rutile titanium dioxide (thin platelet)
3. rutile titanium dioxide (amorphous)
4. anatase titanium dioxide (amorphous).

The particular rutile grade (thick and thin platelet) used in this study was similar in structure to that used in the carcinogenicity study of Bernard *et al.* (1990) summarised below, except that the mica was removed by extraction as described in the manufacturing process.

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The study assessed and compared the absorption, rates and routes of excretion and distribution of titanium in male and female rats after exposure to diet containing platelet forms of rutile titanium dioxide and amorphous forms of rutile and anatase titanium dioxide. Groups of three animals per sex per time-point received either a control control diet or diets containing one of the four types of titanium dioxide treated groups. The four forms of titanium dioxide were incorporated into the diet at a nominal concentration of 200 mg/kg (equivalent to approximately 30mg/kg bodyweight). These diets were fed to rats for seven consecutive days after which the treated diets were replaced by control diet. Groups of animals were sacrificed at 1, 24 and 72 hours after withdrawal from the treated diet for determination by Inductively Coupled Plasma - Atomic Emission Spectrometry (ICP-AES) of the titanium content in tissues (liver, kidneys, muscle and whole-blood) and urine and faeces collected up to 72 hours.

The main route of titanium excretion was via the faeces. The faecal excretion in each collection interval (0 - 24, 24 - 48, 48 - 72 hours) was similar between all titanium dioxide treated groups. The mean total amounts of titanium excreted in the faeces in the 72 hours after withdrawal of the titanium dioxide containing diet were in the range of 1.1-2.2 mg for male rats and 1.1-1.3 mg for female rats. Urinary excretion of titanium was generally below the limit of quantification (<0.04 mg/l). Whole blood concentrations of titanium in all groups were below <0.04 mg/l and concentrations of titanium in liver, kidney and muscle were mainly below the limit of detection (<0.1 - <0.2 mg/kg wet weight) or in the range of 0.1 - 0.3 mg/kg wet weight for most animals treated with either control or titanium dioxide containing diet.

These results indicate that there was no accumulation of titanium in tissues following administration of diets containing 200 mg/kg diet of titanium dioxide, in contrast to earlier studies in which low accumulation of titanium in muscle was reported for rats administered high dietary concentrations of titanium dioxide (100000 mg/kg diet) for at least 30 days (West and Wyzan 1963).

The new bioavailability study showed that essentially there was no difference in the systemic absorption of the four forms of titanium dioxide following dietary administration at a nominal concentration of 200 mg/kg (based on the limit of quantification of <0.04 mg/l for urinary excretion).

Chronic toxicity and carcinogenicity studies in laboratory animals

A NCI carcinogenicity study was conducted in groups of 50 per sex of Fischer 344 rats and B6C3F1 mice dosed at 0, 25000 and 50000 mg titanium dioxide /kg diet for 103 weeks (NCI, 1979). Increased incidences of thyroid C-cell adenomas or carcinomas were observed in female rats but these increases were neither statistically significant nor considered to be related to administration of the test compound. Tumour incidences in the other groups were not significantly higher than in controls. A chronic dietary study administration of titanium dioxide coated mica at 0, 1, 2 and 5% in Fischer 344 rats for 130 weeks showed no toxicological or carcinogenic effects (Bernard *et al.*, 1990).

Discussion

Since there are no significant differences in bioavailability between the different forms of titanium dioxide the toxicity profile should be comparable and can be extrapolated between the forms. The Panel concurred with the JECFA assessment of titanium dioxide and noted that this was supported by the more recent chronic toxicity and carcinogenicity studies.

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Conclusions and Recommendations

The Panel considered that the rutile and anatase forms of titanium dioxide were similar chemically but differed in their crystalline structure and light reflectance. The Panel agreed that the new bioavailability study showed that bioavailability of these forms was essentially the same and that therefore the toxicological database would be applicable to either form. The Panel noted that although estimated exposures were provided for the petitioner's proposed uses of the platelet form of rutile titanium dioxide (confectionery and food supplement tablets in addition to medicinal tablets), the platelet or amorphous form of rutile titanium dioxide could be used to replace anatase titanium dioxide in any of its current applications. The Panel concluded that the use of rutile titanium dioxide in the platelet or amorphous forms would not pose any safety concerns.

Documentation provided to EFSA

Dossier prepared and submitted on behalf of the petitioner (Engelhard) for the evaluation of rutile titanium dioxide, platelet form as a new food additive (Association Management & Regulatory Services, 2004).

An annex containing a number of documents and publications (not all the papers and articles supplied have been referenced in the text as they include reviews and material that were not relevant to the safety assessment).

References

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SCIENTIFIC PANEL MEMBERS

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Table 1.

Summary of Use-Levels and Estimated Intakes for Rutile Titanium Dioxide for the Proposed Food and Medicinal Product Uses in the European Union

Proposed Use	Use-Level	Estimated Intake¹
Medicinal Product Tablet	0.4%	0.25 mg/kg bw/day
Food Supplement Tablet	0.4%	0.625 mg/kg bw/day
Confectionery ²	0.068%	0.407 mg/kg bw/day
Total		1.282 mg/kg bw/day

1. Based on an assumed human body weight of 60 kg.

2. Based on UK consumption data.

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Annex 1. PURITY CRITERIA FOR TITANIUM DIOXIDE.

The anatase and rutile forms of titanium dioxide differ primarily in colour, crystalline form and physical description. All other specifications are the same as listed in the current purity criteria for titanium dioxide E171. Proposed purity criteria for rutile titanium dioxide, platelet form are tabulated below. These differ from the current EU Purity Criteria for titanium dioxide (E171) in altering the description from “amorphous white powder” to “white to slightly coloured powder”.

Analytical data for different manufacturing batches of the thick and thin platelet forms of rutile titanium dioxide, amorphous rutile and anatase titanium dioxide were provided to support the proposed specifications.

SPECIFICATION	REQUIREMENT
Synonyms	CI Pigment White 6
Definition	Titanium dioxide consists essentially of pure titanium dioxide in amorphous or platelet form, which may contain small amounts of alumina and/or silica.
Class	Inorganic
Color Index No.	77891
Einecs	236-675-5
Chemical Name(s)	Titanium dioxide
Chemical Formula	TiO ₂
Molecular Weight	79.88
Assay	Content not less than 99% on an alumina and silica-free basis
Description	White to slightly coloured powder
Identification	
Solubility	Insoluble in water and organic solvents. Dissolves slowly in hydrofluoric acid and in hot concentrated sulphuric acid.
Loss on Drying	Not more than 0.5% (105 ⁰ C, 3 hours)
Loss on Ignition	Not more than 1.0% on a volatile matter free basis (800 ⁰ C)
Aluminium oxide and/or silicon dioxide	Total not more than 2.0%
Matter soluble in 0.5 N HCl	Not more than 0.5% on an alumina and silica-free basis and, in addition, for products containing alumina and/or silica, not more than 1.5% on the basis of the product as sold.
Water soluble matter	Not more than 0.5%
Cadmium	Not more than 1 mg/kg
Antimony	Not more than 50 mg/kg by total dissolution
Arsenic	Not more than 3 mg/kg by total dissolution
Lead	Not more than 10 mg/kg by total dissolution
Mercury	Not more than 1 mg/kg by total dissolution
Zinc	Not more than 50 mg/kg by total dissolution