Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the risk associated with the consumption of food supplements that contain curcumin as an ingredient

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Abstract

The root of the *Curcuma longa* L. botanical species contains certain active components called curcuminoids, with diarylheptanoid structures and consisting of curcumin and analogous compounds, mainly desmethoxycurcumin and bisdesmethoxycurcumin.

Curcumin is a food colour approved for use within the European Union with the code E 100. It provides yellow colouring and is suitable for use in a large variety of products.

In addition to its use as additive in many foods, or its presence in dishes such as curry, currently turmeric, curcuminoids and curcumin are also used as ingredients in many food supplements sold within the European Union.

In its re-evaluation of curcumin as a food additive (E 100), the European Food Safety Authority (EFSA) has set an admissible daily intake (ADI) of 210 mg/day in adults with a body weight of 70 kg.

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Having performed the risk assessment of the consumption of food supplements that contain curcumin as an ingredient, the AESAN Scientific Committee considers that the ADI established for curcumin as an additive is applicable to curcumin as an ingredient in a food supplement, but not to the sum of all curcuminoids, even though curcumin is the main component.

Additionally, it notes that there is no available information on the lack of side effects in children under the age of 18, therefore it would not be desirable to provide food supplements containing curcumin to children under this age.

Similarly, the safety of curcumin as an ingredient in food supplements for pregnant and lactating women has not been established. For this reason, it is not recommended as an ingredient in food supplements for pregnant and lactating women, as curcumin and its metabolites are transferred to infants by their mothers' milk.

It is also recommended that food supplement labels state the amount of curcumin present in their ingredients.

Key words

Curcumin, turmeric, food supplements.

Suggested citation

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1. Introduction

This report is drafted in response to the request of the Spanish Agency for Food Safety and Nutrition (AESAN) for the Scientific Committee to assess the risk associated with consumption of food supplements containing curcumin as an ingredient.

1.1 Chemical composition and active ingredients of turmeric

The botanic species *Curcuma longa* L. is an herbaceous plant of the Zingiberaceae family, native to south-east Asia and with a pantropical and pansubtropical distribution. This plant has a different designation according to the geographic areas where it is used, most commonly known as turmeric or "Indian saffron".

According to the European Pharmacopoeia, the rhizome of turmeric consists of the entire rhizome of *Curcuma longa* L., dried and cured (treated by boiling or steaming), its roots and the external surface of the bark removed, with a minimum content of 25 ml/kg of essential oil and 2 % dicinnamoylmethane derivatives, expressed as curcumin, with respect to the dried drug (EMA, 2018). In this document we shall refer to the turmeric rhizome as turmeric.

Turmeric is chemically comprised of water (13 %), carbohydrates (70 %), protein (6 %), essential oils (6 %), fats (5 %), minerals (3 %), curcuminoids (2-9 %) and traces of vitamins (Soleimani et al., 2018) (Sun et al., 2018).

More than 235 different chemical structures have been identified in turmeric, principally phenolic and terpenoid compounds. These phenolic compounds include 22 diarylpentanoids and diarylheptanoids, and 8 phenylpropenes. The terpenoids are divided into 68 monoterpenes, 109 sesquiterpenes, 5 diterpenes, 3 triterpenes and 4 sterols, as well as 2 alkaloids and another 14 compounds (Almaraj et al., 2017) (Beaume et al., 2018) (Dosoky and Setzer, 2018) (Sun et al., 2018) (Kotha and Luthria, 2019) (Shakeri et al., 2019). The two types of active components of turmeric are curcuminoids and turmeric essential oil.

Curcuminoids, also called curcumins, are diarylheptanoids structures (aryl-C7-aryl skeleton). They are comprised of turmeric (1,7-bis(4-hydroxy-3-methoxyphenyl)-hepta-1,6-dien-3,5-dione) (approx. 77 %) and analogues, principally desmethoxycurcumin (approx. 17 %) and bisdesmethoxycurcumin (approx. 3-6 %) (Figure 1).

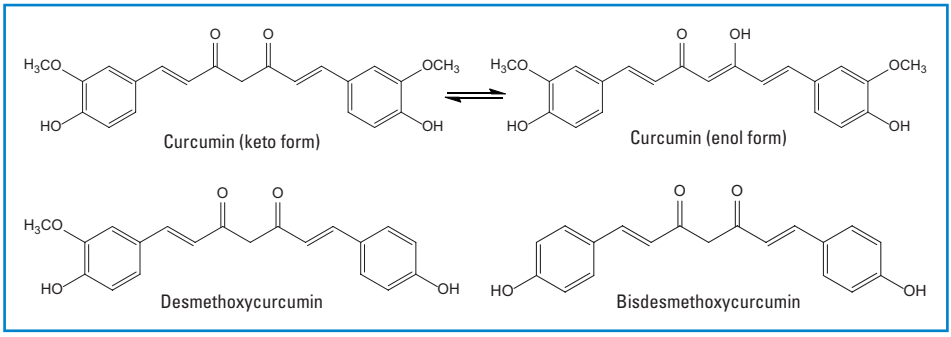

Figure 1. Chemical structures of the principal curcuminoids.

Commercial turmeric usually contains a residue of desmethoxycurcumin (10-20 %) and bis-desmethoxycurcumin (<5 %). The curcuminoid content in turmeric varies from 2-9 % (w/w) depending on the geographic location and cultivation conditions, therefore the standardisations should be specified in food supplements. The curcuminoids are responsible for the yellowish-orange colour of turmeric due to the delocalised electrons in the structure.

Turmeric essential oil (20-70 ml/kg) is rich in terpenic hydrocarbons (α-zingiberene, and α-, β- and δ-curcumene) and sesquiterpene ketones (α-, β-turmerones and atlantones), and is the main reason for the aroma of turmeric (Richmon and Pombo-Villar, 1997). Industrially, turmeric oil is produced during the processing of the oleoresin as a by-product of the extraction of curcumin. This oleoresin, obtained from the rhizome dried and powdered by extraction of solvents, is a dense, earthy, yellowish-orange coloured, semi-solid or pasty, with a performance of approximately 12 %, containing curcuminoids (35-55 %) and volatile oils (≤25 %). After isolating the curcumin from the oleoresin, the matrix extract (approx. 70-80 %) is known as "turmeric oleoresin without curcumin" (Dosoky and Setzer, 2018). In general, turmeric essential oil is obtained from the distillation of the vapour or hydrodistillation of the fresh or dried rhizome. Alternatively, it can also be obtained via extraction using solvents (hexane and other organic solvents), a process that can lead to the loss of volatile compounds during the evaporation of the solvent; or by supercritical fluids with CO_2 from the powdered rhizome (Gopalan et al., 2000) (Manzan et al., 2003).

1.2 Posology of different preparations and commercial products

In application of Article 16d (1) of Directive 2001/83/CE (EU, 2001) on the *Curcuma longa L.* rhizome, a series of herbal preparations and traditional food supplements for oral use for adults and elderly people are identified (EMA, 2018) (Table 1). It is not recommended for use in children and adolescents aged under 18.

Table 1. Definitions and posology of different commercial preparations of turmeric

Definition	Posology
Powdered turmeric	1.5-3 g/day (from 0.5 to 1 g, 2-3 times per day)
Infusion (herbal tea)	0.5-1 g in 150 ml of infused water, 2-3 times per day
Tincture (1:10, ethanol 70 % v/v)	0.5-1 ml, 3 times per day
Tincture (1:5, ethanol 70 % v/v)	10 ml once per day or 5 ml in 60 ml of water 3 times per day
Dry extract (13-25:1, ethanol 96 % v/v)	90-162 mg/day equivalent, in 2 to 5 doses
Dry extract (5.5-6.5:1, ethanol 50 % v/v)	100-200 mg, twice per day

The designations of the available commercial products are (EMA, 2018):

- Whole dried rhizome (Dry extract).
- Turmeric: powder prepared from powdered roots with a certain size mesh (60-80 mesh) (Dry extract).
- Turmeric essential oil: preparation based on powdered rhizome or leaves by supercritical extraction or distillation (Tincture).

- Turmeric oleoresin. Extraction with organic solvents (Dye).

In terms of the situation with food supplements containing curcumin in Spain, a non-exhaustive sampling has been performed of the supplements registered in the AESAN General Health Registry for Food Companies and Foods during the 2017-2019 period (2020). 106 supplements have been identified that contain the term "*curcum**" in their brand name. In this regard, the heterogeneity of the information provided in the label regarding the curcumin content is remarkable, most commonly informed in terms of turmeric content (usually in extract form) and in some cases in terms of curcuminoids or curcumin. There are also supplements that do not provide any information on these compounds, referring only to the presence of turmeric extract among the ingredients.

The highest turmeric content detected in this group of 106 supplements was in a supplement with a maximum recommended dosage of 2100 mg. In addition, 25 of the 106 supplements (24 %) provide information on the curcuminoid content, being 1900 mg the maximum daily amount of that compound established by a manufacturer. In terms of curcumin, only 36 of the 106 supplements (34 %) provide information on its content, with 950 mg and 1.57 mg being the maximum and minimum daily amounts established, respectively.

1.3 Regulation

The regulation of and maximum recommended intake for curcumin differ in some countries and others and also for its use as an ingredient, additive or food supplement.

With respect to food supplements, in Spain they are regulated by Royal Decree 1487/2009 (BOE, 2009) which defines them as "food products whose purpose is to complement regular diet and consists of concentrated sources of nutrients or other substances that have a nutritional or physiological effect, in simple or combined form, marketed in dosage form, that is capsules, lozenges, tablets, pills and other similar forms, sachets of powder, vials of liquid, dropper bottles and other similar liquid and powered forms to be taken as small single doses".

Royal Decree 130/2018 (BOE, 2018) amends Royal Decree 1487/2009, establishing a national list of different substances of vitamins and minerals that can be used in food supplements.

In addition, at European Union Level, Commission Implementing Regulation (EU) 2017/2470 establishes the Union list of novel foods authorised, which includes substances authorised through this procedure for use in food supplements (EU, 2017).

The rest of the substances can be marketed in Spain under the principle of mutual recognition of legal marketing in other European Union Member States. Curcumin is one such case, as it does not currently appear on this list of substances that can be used for the manufacture of food supplements in Spain (BOE, 2018) nor among the ingredients authorised as novel foods for use in supplements (EU, 2017) and its marketing is carried out under this principle of mutual recognition.

Curcumin is also authorised in the European Union as a food colour (E 100), forming part of group III (food colours with maximum individual intake limits or combined in a series of food categories). The maximum authorised limits are 250 mg/kg (or mg/l) for curcumin individually and 500 mg/kg (or mg/l) combined with other group III food colours. The authorised uses as a food colour also include

food supplements (except those used for breast-feeding mothers and young children) with maximum combined limits (group III) for liquid or solid supplements of 100 mg/l and 300 mg/kg, respectively (EU, 2008).

At international level, curcuminoids have been recognised by the FDA (Food and Drug Administration) as safe under the GRAS designation (FDA, 2020).

In terms of intake as a common food, it is notable that, for example, in India the average intake of turmeric is approximately 2-2.5 g/60 kg of weight daily, equivalent to 60-100 mg of curcumin (Amalraj, 2017).

2. Bioavailability

Pharmacokinetic studies in models with rodents and in humans have demonstrated the poor bioavailability of curcumin, due principally to three factors (Toden and Goel, 2017):

- Poor solubility in water.
- Low absorption.
- Rapid metabolism in conjugates.

Several studies have demonstrated the difficulty of curcumin reaching optimal active concentrations due to its poor solubility and poor bioavailability. Curcumin is metabolised principally through reduction and conjugation reactions. Initially it is biotransformed to dehydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin *in vivo* after oral administration in rats and mice, and then in monoglucuronide and monosulphate conjugates (Pan et al., 1999) (Jude et al., 2018).

Curcumin is very unstable in aqueous solutions in physiological conditions. Its principal metabolite, tetrahydrocurcumin is much more stable than curcumin in phosphate buffer 0.1 M at pH 7.2 (37 ºC) (Pan et al., 1999).

It degrades well through nucleophilic addition reactions and through photo-degradation to more soluble structures such as ferulic acid and vanillic acid, among others (Anand et al., 2007).

In the body, the greater part of curcumin is excreted through faeces and small quantities are absorbed in the intestine. Preliminary studies in animals show that curcumin is metabolised and conjugated rapidly in the liver and, subsequently, is excreted in faeces with limited systemic bioavailability.

An intravenous dose of 40 mg/kg of curcumin administered to rats showed a complete plasma clearance 1 hour after dosage. An oral dose of 500 mg/kg administered to rats showed a maximum plasma concentration of just 1.8 ng/ml (Fadus et al., 2017). The oral pharmacokinetic evaluation of curcumin in humans of a dose of 8 g resulted in a plasma concentration of curcumin below 1 µg/ml.

It is clear that curcumin dissolves poorly in aqueous preparations as would be the case of the infusion. The lipophilic nature of curcumin also predisposes it to poor absorption unless ingested with fat extracts.

Several phase 1 clinical trials, principally in patients with colorectal cancer, have reported data on the pharmacokinetics, metabolites and systemic bioavailability of curcumin. In a trial with 25 patients with precancerous lesions that received oral doses of 4, 6 and 8 g/day of curcumin over

3 months, maximum plasma concentrations in the first 2 hours, of just 0.51 ± 0.11, 0.63 ± 0.06 and 1.77 ± 1.87 μM, respectively, were detected, and were found to be safe and tolerable even at 8 g. Urinary excretion of curcumin was undetectable (Cheng et al., 2001). Another study of 15 patients with advanced colorectal cancer reported even lower serum concentrations of curcumin. These patients received 0.45-3.60 g/day of curcumin over 4 months and plasma concentrations were only detected for the highest dosage in 3 of the 6 patients with an average during the first month of 11.1 ± 0.6 nmol/l (Sharma et al., 2004).

However, the lipophilic character of curcumin makes it pass the blood-brain barrier (Ringman et al., 2005) (Darvesh et al., 2012b) (Hügel, 2015) (Reddy et al., 2018). Curcumin conjugates in plasma are responsible for the non-enteric actions. The concentration of conjugate derivatives of curcumin reaches the maximum 1 hour after ingestion and lasts 24 hours later, while non-conjugate derivatives are only detected in traces. The main metabolite present in curcumin, tetrahydrocurcumin, has weak biological activity, clearly lower than curcumin itself, making it especially important to try to avoid the conjugation of the curcumin. In this respect, there are data on the inhibition of curcumin conjugates using piperidine (Shoba et al., 1998).

The bioavailability of curcumin increases when administered orally together with piperine, an alkaloid present in black pepper and long pepper (*Piper nigrum* and *P. longa*) and known inhibitor of hepatic and intestinal glucuronidation. High dose of curcumin (2 g/kg) co-administered orally with piperine increased bioavailability by 154 %.

The plasma levels of curcuminoids are extremely low (<50 ng/ml), even after oral ingestion of up to 12 g/day. This low oral bioavailability makes it very difficult to assess the absorption of curcuminoids through monitoring based on original forms.

Very diverse analytical methods have been developed to determine the chemical composition of different samples of turmeric and curcuminoid formulation, and to trace the metabolism of curcumin in *in vitro* and *in vivo* studies. Through the application of ultra-resolution liquid chromatography coupled with mass spectrometry with quadrupole (UPLC/ESI-Q-TOF-MS), the pharmacokinetics of curcuminoids and their metabolites have been characterised and quantified selectively and sensitively in the human blood plasma of healthy volunteers after oral administration of curcumin and different formulations of curcumin, as a bioavailable form of curcumin prepared using polar non-polar sandwich technology with complete natural turmeric matrix (Jude et al., 2018). In this study it was demonstrated that this matrix increases the concentration of tetrahydrocurcumin, hexahydrocurcumin, octahydrocurcumin, curcumin-o-glucuronide and curcumin-O-sulphate in blood plasma after administering the product.

Numerous studies have also been carried out to increase the bioavailability and activity of curcumin (Del Prado-Audelo., 2019), with new administration systems, including the use of nanoparticles, liposomes, polymeric micelles, complexes with transition metallic ions and complexes with phospholipid complexes or adjuvants like piperine, that interfere with glucuronidation, and the use of curcumin structural analogues (Aggarwal, 2008). Similarly, Purpura et al. (2018) reported that the new formulation of curcumin γ-cyclodextrin (CW8) can increase oral bioavailability up to 39 times in comparison with the standardised extract of curcumin not formulated with cyclodextrin. In other

clinical trials, the micellar formulation shows a significant improvement in the oral bioavailability of 80 mg of curcumin in healthy humans (88 times) in relation to native curcumin. Theracurmin is a synthetic derivative of curcumin in the form of nanoparticles with a much greater bioavailability. Hasan et al. (2019) have encapsulated curcumin in nanoliposomes and nanoliposomes covered with chitosan in an attempt to simulate the gastrointestinal environment, observing that the second formulation exhibits a more stable and prolonged release of curcumin in comparison with uncovered nanoparticles, especially in gastric fluid, demonstrating that they are efficient release systems of poorly soluble lipophilic compounds with very low oral bioavailability. These studies show promising results for overcoming the low absorption, rapid metabolism and scant bioavailability of curcumin.

Despite the fact that its efficacy has been studied against a number of health problems, clinical application is limited due to problems that include low solubility in water, low oral bioavailability, low intestinal absorption and rapid metabolism in the gastrointestinal tract. Even at high doses of 12 g/day, absorption of the compound is insignificant (Nguyen, 2017).

It is clear that the bioavailability and bioactivity of curcumin will depend on the format in which it is presented and/or the physicochemical form in which this bioactive ingredient is found.

3. Biological activity and safety

Most of the biological effects of turmeric are attributed to the presence of curcuminoids, principally curcumin, and essential oil. Curcumin could exercise enteric and non-enteric effects due to potential antioxidant and inflammation reduction activities.

A multitude of clinical studies have been carried out with turmeric root extracts or with curcuminoids to study its possible application for several pathologies.

The European Medicines Agency (EMA, 2018) and the Spanish Agency of Medicines and Medical Devices (AEMPS, 2020) approve its traditional use to increase biliary secretion in the treatment of indigestion: feeling of fullness, flatulence and slow digestion.

The safety and efficacy of curcumin has been studied in several trials with humans. In this regard, safety studies with scaled dosage indicated that curcumin was safe in doses as high as 12 g/day over 3 months (Gupta et al., 2013). More recently, it has been described that curcumin taken orally is not toxic to humans up to 8 g/day over 3 months (Sun et al., 2018).

However, some adverse effects were reported (Table 2). The most frequent adverse effects (nausea, abdominal pain, flatulence, gastric irritation and diarrhoea) are foreseen and to be expected as they are an increased response to its activity and depend on the dose (produced at high doses). They are not usually serious or mortal (Hewlings and Kalman, 2017) (EMA, 2018).

Other adverse effects have also been described such as obstruction of bile ducts, cholangitis, gallstones and other biliary alterations. In susceptible individuals, the risk of renal lithiasis can also increase (EMA, 2018).

Table 2. Studies in humans on the adverse toxic effects of curcumin

Type of trial	Compound	Dose and treatment time	Characteristics of trial	Effects (*)	Reference
Clinical trial, phase 1 (sick patients)	500 mg curcumin tablets, with 99.3 % purity	Repeated doses: 500, 1000, 2000, 4000 and 8000 mg/day over 3 months. The dosage changes from one to the next when less than one third (3 to 6 patients) at this level of dosage do not experience toxicity above grade 1 over the 3 months of treatment	High-risk patients or those with premalignant lesions (neoplasms, resected bladder cancer)	The results did not reveal toxicity related to the treatment up to 8000 mg/day over 3 months. It was not possible to administer a greater dosage of curcumin due to the large volume of the curcumin tablets	Hsu and Chen (2007)
Clinical trial, phase 1 (sick patients)	Turmeric extract: gelatin capsule of 220 mg with 20 mg of curcuminoids (18 mg curcumin + 2 mg of desmethoxycurcumin + 200 mg of essential oil extracted from *Curcuma* spp). Essential oil: turmerone, atlantone, zingiberene	Repeated doses: from 440 mg of turmeric extract (equivalent to 36 mg curcumin) up to 2200 mg of turmeric extract (equivalent to 180 mg curcumin)/day over 4 months	3 patients/dose. Patients with colorectal cancer resistant to conventional chemotherapy	The drug was well tolerated with the following exceptions: 1 patient on 1320 mg of turmeric extract daily experienced grade 1 nausea; and 2 patients (1 on 880 mg and the other on 2200 mg of turmeric extract daily) developed grade 1 and grade 2 diarrhoea, respectively	Hsu and Chen (2007)
Clinical trial, phase 1 (sick patients)	500 mg capsule of curcuminoids containing: 450 mg of curcumin + 40 mg de desmethoxycurcumin + 10 mg of bisdesmethoxycurcumin	Repeated doses of curcumin: 450, 900, 1800 or 3600 mg per day over 4 months	15 patients with refractory colorectal cancer	Well tolerated with exceptions: 3 patients with minor gastrointestinal adverse effects (grade 1 diarrhoea and grade 2 nausea). Increase of levels of serum alkaline phosphatase and serum lactate dehydrogenase (compatible with grade 1-2 toxicity) in 4 and 3 patients, respectively	Hsu and Chen (2007)

Table 2. Studies in humans on the adverse toxic effects of curcumin

Type of trial	Compound	Dose and treatment time	Characteristics of trial	Effects (*)	Reference
Healthy volunteers	Capsule with standardised *Alleppey finger turmeric* powder extract. Composition of capsule: 95 % of three curcuminoids: 75 % curcumin + 2 % bisdesmethoxycurcumin + 23 % desmethoxycurcumin	Single oral dose (acute toxicity): between 500 and 12 000 mg. Safety was evaluated 72 hours after administration of curcumin	24 healthy volunteers	7 individuals developed diarrhoea, headache, skin rash and yellow-coloured stool, all grade 1 effects and not related to the dosage. The maximum tolerated dose of curcumin was not reached because the doses of more than 12 000 mg were unacceptable for the patients due to the large size of the capsules	Hsu and Chen (2007)
Healthy volunteers	Turmeric oil: 0.2 ml gelatin capsule containing 59 % turmerone and arturmerone, 25 % zingiberene, 1 % cineole, 1 % d-phellandrene, 0.6 % d-sabinene; 0.5 % borneol + α and β atlantone and sesquiterpene alcohol	Dose: - 1st month: three intakes of 0.2 ml= 0.6 ml of oil/day. - 2nd and 3rd month: 1 ml/day in 2 doses of 0.4 ml (morning and night) + 1 dose of 0.2 ml (evening)	9 healthy patients (aged 20 to 33): 4 men and 5 women. 2 patients left the study, one due to an allergic reaction and the other due to fever caused by tuberculosis	No volunteer developed adverse effects. All maintained normal pulse, arterial pressure and weight throughout the study period; no lymphadenopathy or hepatosplenomegaly was detected and there were no changes in the menstrual pattern of female volunteers. Only in one case was an allergic reaction of skin rash to the preparation observed	Joshi et al. (2003)
Clinical trial, phase 1 (sick patients)	500 mg curcumin tablets	Doses: 500, 1000, 2000, 4000, 8000 and 12 000 mg/day over 3 months	24 high-risk patients (neoplasms, resected bladder cancer): 25 patients (13 men and 12 women) aged 36-77	There is no toxicity related to the treatment up to 8000 mg/day over 3 months. It was not possible to administer a greater dosage of curcumin due to the large volume of the curcumin tablets	Cheng et al. (2001)
Sick patients	500 mg curcuminoids capsules. Composition of capsule: 450 mg curcumin + 10 mg bisdesmethoxycurcumin + 40 mg desmethoxycurcumin	Doses: 1, 2, 4 or 8 capsules per day (450, 900, 1800 or 3600 mg/day) over 24 months	15 patients with colon or rectal adenocarcinoma. Over the age of 18	Nausea and diarrhoea. 4 patients: increase in content of serum alkaline phosphatase. 3 patients: increase (>150 %) of the lactate dehydrogenase	Sharna et al. (2004)

Table 2. Studies in humans on the adverse toxic effects of curcumin

Type of trial	Compound	Dose and treatment time	Characteristics of trial	Effects (*)	Reference
Sick patients	Curcumin	1200 mg/day over 2 weeks	18 patients with rheumatoid arthritis (aged 22 to 48)	No adverse effects or significant changes in arterial pressure, pulse, erythrocyte sedimentation rate or renal or liver function	Chainani-Wu (2003)
Post-surgery patients	Curcumin	5 days duration, three groups: - Placebo. - Curcumin (1200 mg/day). - Phenylbutazone (300 mg/day)	45 post-surgery patients	One patient in the curcumin group complained of mild temporary dizziness on the third post-surgery day	Hsu and Cheng (2007)
Sick patients	Curcumin	2500 mg/day	19 patients with AIDS	Two patients: gastric irritation, one of whom had a history of peptic ulcers. No other adverse reaction was observed, and blood analysis showed no adverse effects	Chainani-Wu (2003)
Sick patients	Curcumin isolated from *Curcuma longa* rhizomes (95 % purity). Gelatin capsules were filled with 375 mg	375 mg three times per day over 6 to 22 months	5 patients with idiopathic orbitary inflammatory pseudotumor (aged 6 to 54)	No adverse effects were observed in any patient	Lal et al. (2000)
Sick patients	500 mg tablets (20 % mix of natural curcuminoids, 40 % phosphatidylcholine and 40 % microcrystalline cellulose). The mix of curcuminoids contains: 75 % curcumin + 10 % bisdesmethoxycurcumin + 15 % desmethoxycurcumin	200 mg curcumin/day: one tablet after breakfast and another after dinner	100 patients with osteoarthritis in the knee (grade 1 or 2)	No adverse effects were observed	Belcaro et al. (2010)

Table 2. Studies in humans on the adverse toxic effects of curcumin

Type of trial	Compound	Dose and treatment time	Characteristics of trial	Effects (*)	Reference
Sick patients	Curcumin formulation in capsules	Three groups: - I: 500 mg curcumin. - II: 500 mg curcumin + 50 mg diclofenac sodium. - III: 50 mg diclofenac sodium Treatment: two capsules/day over 8 months	45 patients (38 women and 7 men) with active rheumatoid arthritis (grade 1 or 2). Aged between 18 and 65	Curcumin was generally safe and well tolerated in the majority of individuals over 8 weeks. The adverse effects evidenced in the curcumin group were mild fever and throat infection	Chandran and Goel (2012)
Healthy and sick patients	Solid lipid curcumin particle (SLCP) and 95 % curcuminoid extract (>60 % curcumin)	Sick individuals: SLCP administered in capsules, with oral dose of 2000 mg (400-600 mg curcumin), 3000 and 4000 mg. Healthy individuals: a single oral dose in 650 mg capsule, containing 130-195 mg of SLCP curcumin or > 390 mg of curcumin of the extract with 95 % curcuminoids is administered. Treatment over 8 weeks	11 patients with osteosarcoma (7 men and 4 women) aged 12 to 60. 6 healthy men aged 18 to 40	No adverse effects were observed after the single oral administration of SLCP in healthy volunteers or in patients with osteosarcoma	Gota et al. (2010)

(*) Degrees (general definitions) 0= no adverse effect or within normal limits; 1= mild adverse effect; 2= moderate adverse effect; 3= serious and undesirable adverse effect; 4= potentially mortal or incapacitating adverse effect; 5= adverse effect is related to death.

However, Smith and Ashar (2019) documented the first case of anaemia due to iron deficiency associated with the consumption of a turmeric supplement. While the causality cannot be easily determined, the patient's haemoglobin, iron and ferritin levels fell after beginning to ingest turmeric and returned to normal when interrupted. After an exhaustive evaluation, no other cause of iron deficiency or blood loss was found. The stoichiometric properties of curcumin indicate that it could adhere almost all the absorbable iron, bind to ferric iron (Fe^{3+}) to form a ferric-curcumin complex that is dose-dependent and cause iron deficiency (Smith and Ashar, 2019), therefore the consumption of turmeric and/or curcumin would not be advisable, except in the case of hemochromatosis, in stages of life when good iron supply is necessary, such as in the case of those under 18.

Furthermore, in a trial carried out with animals, curcumin removed the hepatic hepcidin synthesis, one of the regulator peptides of the metabolism of iron as well as the expression of ferritin, and iron concentration in the liver and spleen fell by more than 50 % (Naz and Lough, 2014).

Two cases of severe hepatitis induced by a turmeric food supplement have also been described (Luber et al., 2019) (Table 3).

Table 3. Case reports on the adverse effects of turmeric

Case	Dose and treatment time	Patient history	Adverse effects	Reference
Anaemia due to iron deficiency	Medication + six capsules of turmeric extract (6 x 538 mg) per day over 2 months (*)	Osteoarthritis, prostate cancer	Iron, ferritin and haemoglobin levels consistent with iron deficiency. 2 weeks after cessation of the turmeric supplement and continuing with an iron supplement (28 mg elemental iron/twice daily), the values returned to normal	Smith and Ashar (2019)
Hepatotoxicity	Medication + turmeric supplement (375 mg curcuminoids and 4 mg black pepper) per day over 1 month. All treatment was suspended for 2 months. Only the turmeric supplement was restarted (1125 mg curcuminoids) daily for 3 weeks	Oligoarticular osteoarthritis	Nausea, pruritus, jaundice, pale stools, dark urine, liver damage and high bilirubin levels after 1 month of supplement + medication. All treatment was ceased and after 2 months liver function had recovered. Only ingestion of supplement was restarted and 3 weeks later nausea was repeated and acute hepatitis was diagnosed. 2 months after ceasing ingestion of the supplement, liver function returned to normal	Luber et al. (2019)

Table 3. Case reports on the adverse effects of turmeric

Case	Dose and treatment time	Patient history	Adverse effects	Reference
Hepatotoxicity	Medication + turmeric supplement for 5 months. Composition and dose not indicated	Osteoarthritis, gout, idiopathic thrombocytopenic purpura and high blood pressure	Liver function normal but 5 months after beginning ingestion of the supplement with turmeric, acute hepatitis and diffuse steatosis appeared. Suspicion of interaction with medication and turmeric supplement was withdrawn. Liver function normal 4 months later	Luber et al. (2019)

(*) The ingestion of 6 x 538 mg per day of curcumin (3228 mg/day) is 46 times the ADI set by the EFSA (for the additive) of 3 mg/kg b.w./day equivalent to 210 mg curcumin/day for an adult weighing 70 kg.

With respect to turmeric essential oil, it must be noted that there are fewer studies available compared to curcuminoids. Nonetheless, in one human study in which turmeric essential oil was administered orally, no haematotoxicity, nephrotoxicity or hepatotoxicity was observed at 1 month and 3 months (Joshi et al., 2003).

In a study in animals evaluating acute and subchronic toxicity, and the mutagenic effect of turmeric essential oil, no mortality, adverse clinical signs or changes in body weight or in the amounts of food consumed, were observed (Liju et al., 2013).

There are a number of studies on *in vivo* and *in vitro* toxicity of curcumin, commercial preparations that incorporate curcumin in micro and nanoparticles, and their adverse effects (Table 4).

Table 4. Adverse *in vivo* and *in vitro* effects of curcumin, its commercial preparations and preparations based on micro and nanoparticles

Type of trial	Compound	Species, dose and treatment time	Results	Reference
In vivo				
Acute toxicity	Preparation of solid lipid curcumin particle. The turmeric root extract that contains curcumin was mixed with soy lecithin containing purified phospholipids, docosahexaenoic acid (DHA), stearic vegetable oil and inert ingredients	Two studies were carried out in accordance with the OECD protocol no. 420 (15 days observation). Species: 1st: Wistar rats and 2nd: Swiss albino mice	Turmeric is safe. Acute toxicity trial: DL_{50}> 2000 mg/kg b.w./day (*)	Dadhaniya et al. (2011)
Acute toxicity	Curcumin and curcumin incorporated to titanium dioxide nanoparticles (CTNP)	Male Sprague Dawley rats. Treatment with curcumin or CTNP: group I (control). Biodistribution trial: group II (20 mg/kg b.w.). Toxicity trial: group IIa (1 mg curcumin/kg b.w.), group IIb (20 mg curcumin/kg b.w.), group IVa (5 mg CTNP/kg b.w.), group IVb (10 mg CTNP/kg b.w.)	CTNP is distributed better than curcumin. Neither curcumin nor C caused toxicity. The liver (350 µg/organ) and kidneys (300 µg/organ) are the organs that accumulate the most curcumin. No change to blood parameters (SGPT, SGOT, LDH) or alteration of blood cells. Does not cause alteration in the double helix of DNA (comet assay)	Sherin et al. (2017)
Acute toxicity	Nanoparticles of iron oxide covered with curcumin (Cur-IONPs)	Male Balb/c mice (5/group). Time of study: 0.5 hours, 1 hour, 2 hours, 1 day, 2 days, 1 week, 2 weeks and 3 weeks. IV Administration of 5 mg/kg b.w. through the vein in the tail	Blood biochemical parameters of Cur-IONPs: they increase from the injection and are stabilised after 1 day (serum albumin, serum urea, creatinine, and uric acid) or in weeks 2-3 (ALT, AST, glucose, iron)	Elbialy et al. (2019)
Acute toxicity	Magnetic nanoparticles (Fe_3O_4) covered with polyethylene glycol curcumin (PEG-Cur): MNP-PEG-Cur	7 mice (male and female). Haemolytic trial: Dose: 10 mg MNP-PEG-Cur/ml	Haemolytic trial: haemolysis was <5 %. It is considered a non-haemolytic compound	Ayubi et al. (2019)
Short-term toxicity and subchronic toxicity	Turmeric oleoresin (79-85 % curcumin)	B6C3F1 mice (10/sex/dose). Study time: 13 weeks (91 days). Curcumin doses: - Males: 0, 150, 750, 1700, 3850 mg/kg b.w./day. - Females: 0, 200, 1000, 1800, 4700 mg/kg b.w./day	NOAEL= 7700 mg/kg b.w./day (males) and 9280 mg/kg b.w./day (females)	EFSA (2010) (reference National Toxicology Program, 1993)

Table 4. Adverse *in vivo* and *in vitro* effects of curcumin, its commercial preparations and preparations based on micro and nanoparticles

Type of trial	Compound	Species, dose and treatment time	Results	Reference
Short-term toxicity and subchronic toxicity	Turmeric oleoresin (79-85 % curcumin)	F344 rats (10/sex/dose). Study time: 13 weeks (91 days). Curcumin dose: - Males: 0, 50, 250, 480, 1300, 2600 mg/b.w./day. - Females: 0, 60, 300, 550, 1450, 2800 mg/kg b.w./day	NOAEL= 1300 mg/kg b.w./day (males) and 1450 mg/kg b.w./day (females)	EFSA (2010) (reference National Toxicology Program, 1993)
Chronic toxicity	Preparation of solid lipid curcumin particles. The turmeric root extract that contains curcumin was mixed with soy lecithin containing purified phospholipids, docosahexaenoic acid (DHA), stearic vegetable oil and inert ingredients	Wistar rats (10/sex/group). Treatment time: 90 days. Doses: group I (control), group II (180 mg/kg b.w./day), group III (360 mg/kg b.w./day), group IV (720 mg/kg b.w./day). Recovery study (90 days treatment + 28 days without treatment): group V (control), group VI (720 mg/kg b.w./day)	Curcumin is safe. Chronic toxicity trial: no adverse effects were observed in male or female rats. They propose a NOAEL of 720 mg/kg b.w./day (the highest dose tried)	Dadhaniya et al. (2011)
Chronic toxicity and carcinogenesis	Turmeric oleoresin (79-85 % curcumin)	B6C3F1 mice (60/sex/dose). Study time: 103 weeks (721 days). Curcumin doses: - Males: 0, 220, 1520, 6000 mg/kg b.w./day. - Females: 0, 320, 1620, 8400 mg/kg b.w./day	No incidence of tumours observed	EFSA (2010) (reference National Toxicology Program, 1993)
Chronic toxicity and carcinogenesis	Turmeric oleoresin (79-85 % curcumin)	F344/N rats (60/sex/dose). Study time: 103 weeks (721 days). Curcumin dose: - Males: 0, 80, 460, 2000 mg/kg b.w./day. - Females: 0, 90, 440, 2400 mg/kg b.w./day	Curcumin did not show any carcinogenic effect, but it showed intestinal irritation. A NOAEL of 440 mg/kg b.w./day is determined for the gastrointestinal effect evidenced	EFSA (2010) (reference National Toxicology Program, 1993)

Table 4. Adverse *in vivo* and *in vitro* effects of curcumin, its commercial preparations and preparations based on micro and nanoparticles

Type of trial	Compound	Species, dose and treatment time	Results	Reference
Chronic toxicity: reproductive toxicity	Curcumin (*)	Wistar rats (30/sex/dose). Reproductive toxicity (two generations) protocol of the OECD No. 416. Preliminary study (for selection of dose in definitive study): 28 days. Administered doses: 0, 1500, 3000 or 10 000 ppm. Definitive study: Study time: 21 weeks (F0) and 24 weeks (F1) Doses during study: - Males: 0, 130-140, 250-290, 850-960 mg/kg b.w./day. - Females: 0, 160, 310-320, 1000-1100 mg/kg b.w./day	No changes were observed in progenitors (F0), in their organs or in offspring (F1 and F2). In offspring (F2), a reduction of body weight was observed. They determine: - NOAEL F0= 847 mg/kg b.w./day (males) and 959 mg/kg b.w./day (females). - NOAEL F1= 1043 mg/kg b.w./day (males) and 1076 mg/kg b.w./day (females). - These data were considered by JECFA to determine the ADI of curcumin between 0-3 mg/kg b.w. of 250-320 mg/kg b.w. and a safety factor of 100	Ganiger et al. (2007)
In vitro				
Acute toxicity	Curcumin	Primary cells of human skin fibroblasts (Normal HDFa) and cells established MCF-7 (human breast cancer cells). Concentrations tested: 0, 2.5; 5, 10, 20, 40 and 80 µM. Exposure time 24, 48 and 72 hours	HDFa cells more sensitive to curcumin than MCF7. It was observed that: - Concentrations ≥ 20 µM reduce cellular viability (38-57 %). - Concentrations ≥ 10 µM reduce cellular proliferation. Due to the fact that curcumin inhibits S-glutathionylation of the histone H3, contributing to the halting of mitosis (phase G2/M). Curcumin also increases glutathione levels (GSH)	Cianfruglia et al. (2019)

Table 4. Adverse *in vivo* and *in vitro* effects of curcumin, its commercial preparations and preparations based on micro and nanoparticles

Type of trial	Compound	Species, dose and treatment time	Results	Reference
Acute toxicity	Curcumin	Primary cells: four lines of human astrocytes, D54-MG and A172 (both grade IV), U373-MG and T98G (both grade III). Cell established: SVGp12 (immortalised human astrocytoma). Concentration: 100 µM. Exposure time: 24 hours	IC_{50}> 100 µM. Increase of gall bladders, and maintenance of nuclear integrity (no death due to necrosis, apoptosis or autophagy)	Romero-Hernández et al. (2013)
Acute toxicity	Curcumin, titanium dioxide nanoparticles (TNP) and curcumin incorporated to titanium dioxide nanoparticles (CTNP)	THP1 cells (human monocytes) and H9c2 (cardiomioblasts). Treatment with curcumin or CTNP: group I (control). Toxicity trial: group II (100 ng curcumin), group III (500 ng curcumin), group IV (50 ng TNP), group V (100 ng TNP), group VI (100 ng CTNP) and group VII (200 ng CTNP)	No morphological changes or toxic effects were observed on the doses trialled	Sherin et al. (2017)
Acute toxicity	Curcumin (CUR) encapsulated in cyclodextrin nanosponge (CDNS)	Non-cancerous breast cells (MCF 10A) and 4T1 (invasive breast cells of mouse). Concentrations: 0, CDNS2-CUR, CDNS4-CUR, CDNS8-CUR and CUR (0.1-100 µg/ml). Exposure time 24 and 48 hours	The most sensitive cells were the 4T1s. Toxicity is greater at 24 hours than at 48 hours. CUR presents a reduction of cellular viability from 0.01 µg/ml. The capsules present the same cytotoxicity from 50 µg/ml (MCF 10A) and from 1 µg/ml (4T1)	Gholibegloo et al. (2019)
Acute toxicity	Magnetic nanoparticles (Fe_3O_4) covered with polyethylene glycol curcumin (PEG-Cur): MNP-PEG-Cur	MCF-7 cells (human breast cancer). Curcumin concentrations: 5, 10, 50 and 100 µg/ml, MNP-PEG-Cur. Exposure time: 72 hours	DL_{50} of curcumin: 10-50 µg/ml. DL_{50} de MNP-PEG-Cur: >100 µg/ml	Ayubi et al. (2019)

(*) 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. ALT: alanine aminotransferase; AST: aspartate aminotransferase; DL_{50}: dose that causes death in 50 % of the study population; IC_{50}: concentration that inhibits cellular growth of 50 % of the study population; LDH: lactate dehydrogenase; NOAEL: no observable adverse effect level; b.w.: body weight; SGPT (serum glutamic-pyruvic transaminase or ALT); SGOT (serum glutamic-oxaloacetic transaminase or AST).

The safety of curcumin was subject to evaluation by JECFA (Joint FAO/WHO Expert Committee on Food Additives), which established an acceptable daily intake (ADI) of 0-3 mg/kg b.w./day, that is, 210 mg curcumin/day for an adult weighing 70 kg (JECFA, 2004). The NOAEL value (no observable adverse effect level) in all studies carried out is higher than that used to establish the ADI (Table 3). This is justified by the adverse gastrointestinal effects at 440 mg/kg b.w./day observed in another trial. JEFCA maintained a conservative stance when establishing an ADI of 3 mg/kg b.w./day, ensuring the safety of use of the additive.

Subsequently, the European Food Safety Authority (EFSA) reassessed the safety of curcumin as an additive (E 100) based on the emergence of new scientific evidence of potential toxicity in *in vitro* and *in vivo* trials. In line with the evaluation carried out by JECFA previously, EFSA maintained the ADI of 3 mg/kg b.w./day, based on a NOAEL of 250-320 mg/kg b.w./day (reproductive toxicity) (EFSA, 2010). It also established that curcumin intake in the diet of the general population is equivalent to less than 7 % (0.1 mg/kg b.w./day) of the ADI. However, it highlighted that, considering a scenario of maximum use levels, the intake estimates (mean and P95), in the case of children aged 1 to 10 were above the ADI in some European countries (EFSA, 2010).

Based on these conclusions, EFSA subsequently carried out a more precise exposure assessment, considering new data provided by the industry and European Union Member States (EFSA, 2014). The new evaluation estimated that, for the child and adolescent population, intakes (mean and P95) were below those determined in 2010.

In the study carried out by the EFSA (2014), different scenarios were considered; one more *conservative*, where to determine the consumer's exposure to curcumin over a lifetime, the maximum concentration of curcumin permitted by legislation in each category of food (MPL) was considered; and another more realistic scenario where the average concentration of curcumin in all food categories was applied when their concentration was analytically determined.

Taking into account the high exposure (conservative) scenario, considering the maximum permitted limits, intakes remained above the ADI for these population groups (children and adolescents) (Table 5). However, considering the average concentration (more realistic scenario) all intakes were below the established ADI (Table 6).

Table 5. Summary of estimated exposure to curcumin additive (E 100) considering a scenario of exposure based on the regulatory maximum level of curcumin

Exposure (mg/kg b.w./day)	Children (12-35 months)	Children (3-9 years)	Adolescents (10-17 years)	Adults (18-64 years)	Elderly (> 65 years)
Mean	0.9-3.9	0.9-3.2	0.3-1.6	0.3-1.1	0.1-0.6
P95	2.8-7.2	2.0-6.7	1.0-3.3	0.7-2.3	0.5-1.4

Source: (EFSA, 2014).

Table 6. Summary of estimated exposure to curcumin additive (E 100) considering a scenario of exposure based on the average levels of curcumin found in all categories of food established

Exposure (mg/kg b.w./day)	Children (12-35 months)	Children (3-9 years)	Adolescents (10-17 years)	Adults (18-64 years)	Elderly (> 65 years)
Mean	0.1-0.8	0.2-0.6	0.1-0.3	0.1-0.2	0.03-0.2
P95	0.5-1.2	0.5-1.2	0.2-0.7	0.2-0.5	0.1-0.4

Source: (EFSA, 2014).

The principal categories of foods with high exposure to curcumin (according to Table 5) are:

- Children aged 12-35 months: fine bakery foods and flavoured fermented milk products.
- Children aged 3-9 months: flavoured drinks, fine bakery foods and flavoured fermented milk products.
- Adolescents (10-17 years): fine bakery foods and flavoured drinks.

As a principle of precaution and in accordance with the EMA, there are no data on adverse effects on those aged under 18 (EMA, 2014a, b). It would not be appropriate, therefore, to provide food supplements containing curcumin to those aged under 18 years.

The ADI has been established for curcumin regardless of whether it is consumed as an additive or as an ingredient in food or as a food supplement. It is not applicable to the mix of curcuminoids. Nevertheless, in relation to curcuminoids, the percentage of curcumin is very high in the mix (79-85 %), therefore the other compounds will not significantly increase exposure.

For this reason, the competent authorities in some European Union Member States have issued alert notifications and prohibited the trade of food supplements with curcumin in which the maximum recommended daily amount would exceed the ADI for curcumin.

4. Interactions

Experimental studies have demonstrated that the oral administration of 100 mg/kg of curcumin over 7 days in rats affects the pharmacokinetics of the oral anticoagulant warfarin and the platelet antiaggregant clopidogrel but not the pharmacodynamic parameters (Liu et al., 2013). However, curcumin and its derivative bisdesmethoxycurcumin demonstrated *in vivo* anticoagulant effects upon prolonging the activated partial thromboplastin time and the prothrombin time, and inhibiting the generation of thrombin and the Xa factor. This means that daily consumption of curcumin could help maintain the anticoagulant state (Kim et al., 2012).

Turmeric can interact with oral antagonists of vitamin K such as fluindione, resulting in the elevation of the International Normalized Ratio for prothrombin time (INR) which allows for the evaluation of the risk of bleeding or the coagulation status of the patient (Daveluy et al., 2014).

Data from *in vitro* studies, animal experiments or individual case reports, indicate the possible interaction between curcumin and some drugs such as nonsteroidal anti-inflammatories (NSAIDs), platelet antiaggregants, antihyperlipidemic, antidepressants, antihistamines, antibiotics and chemotherapeutic agents. It can induce pharmacokinetic changes, such as Cmax and the area under the

curve (AUC) which describes the concentration of the drug in the blood based on time, due to the inhibition of isoenzymes of cytochrome (CYP450) and P-glycoprotein (Bahramsoltani et al., 2017).

On the contrary, some trials in humans have demonstrated that curcumin does not interact with cytochrome CYP450, specifically the isoenzymes CYP2C9 and CYP3A4, nor UDP-glucuronosiltransferase (UGT), but is capable of inducing CYP1A2, which could reduce plasma concentration of antidepressants and anti-psychotics (Asher et al., 2017). Nevertheless, further studies are necessary to confirm the clinical relevance of these interactions.

5. Allergies

The most documented reactions to curcumin are contact dermatitis and hives from culinary use or use in cosmetics as an antioxidant (Chaudhari et al., 2015) (Fadus et al., 2017). In India, *kurkum* (turmeric-based dye) is used for religious reasons and to indicate marital status. There are numerous publications on contact dermatitis caused by *kurkum*. Nevertheless, this colouring contains a large number of ingredients and the allergic effect has not been specifically associated with curcumin (Surendranath, 2006) (Chaudhari et al., 2015).

Different publications have described sensitivity to curcumin after topical use in different situations (Table 7) (Chaudhari et al., 2015) (Fadus et al., 2017). In general, possible allergies may be interpreted as anecdotal, given the extended use of this spice as a food and as an additive. However, allergic or immunological reactions are extremely rare.

Table 7. Most common allergic reactions to exposure to turmeric or its derivatives

Compound	Characteristics	Adverse effects	Reference
Turmeric	Topical skin medication	Worsening of base dermatitis	Hata (1997)
	Manipulation of capsules with turmeric (workplace toxicity)	Contact urticaria (presence of IgE)	Liddle et al. (2006)
	Discomfort upon coming into contact with or eating the spice	Contact urticaria	Liddle et al. (2006)
	Patient with pathology and complex treatment of fat absorption therapy. Self-administration of large quantities of turmeric	Anaphylactoid reactions	Adamski et al. (2010)
Tetrahydrocurcuminoid	Cosmetic protection cream	Dermatitis	Lamb and Wilkinson (2003)
Turmeric oil	Used as massage oil	Contact dermatitis	López-Villafuerte and Clores (2016)
Turmeric essential oil	-	Erythema multiforme	Huber et al. (2016)

Conclusions of the Scientific Committee

The AESAN Scientific Committee, having completed the evaluation of the risk associated with the consumption of food supplements containing curcumin as an ingredient, has reached the following conclusions:

- The acceptable daily intake (ADI) has been set by the European Food Safety Authority (EFSA) at 210 mg/day for an adult with a body weight of 70 kg in its reassessment opinion of the food additive curcumin (E 100).
- The ADI established by the EFSA for the additive is applicable to curcumin as an ingredient in a food supplement but not for the sum of all curcuminoids, even though curcumin is the majority component.
- As a precautionary principle and according to the European Medicines Agency (EMA), there is no information on the absence of adverse effects of turmeric on those aged under 18.
- Due to the effects of turmeric as an iron chelator, it would not be appropriate to provide food supplements containing curcumin to those aged under 18.
- The safety of curcumin as an ingredient in supplements during pregnancy and breastfeeding has not been established.
- Its consumption as an ingredient in food supplements during pregnancy and breastfeeding is not recommended, as curcumin and its metabolites transfer via breast milk to infants.
- It is recommended that the labelling of food supplements indicate the quantity of curcumin in its ingredients.

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