Bundesinstitut für Risikobewertung

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Curcumin in food supplements: Acceptable daily intake may be exceeded

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Turmeric or curcumin is not only known as a spice or as a food additive (E100). Food supplements can also contain components of the rhizome of the curcuma plant, often in the form of curcumin-enriched extracts. In addition, piperine or piperine-enriched extracts from pepper may also be added to these products. Piperine can increase the bioavailability of curcumin so that curcumin can be better absorbed by the body.

Within the context of the evaluation of curcumin as a food additive (E100), the European Food Safety Authority (EFSA) has derived an acceptable daily intake (ADI) for curcumin of 3 mg/kg body weight (bw) and day. The ADI specifies the quantity of a substance that can be consumed on a daily basis over an entire lifetime without a detectable risk to health. The German Federal Institute for Risk Assessment (BfR) has used this value as a basis for the assessment of health risks from curcumin in food, in particular from curcumin-enriched food supplements. In the long term, the total intake of curcumin from all sources should not exceed 3 mg/kg bw per day. Besides food supplements, curcumin sources can also be food additives or spices. If this value is exceeded over a longer period of time, even slightly, adverse health effects may occur. This applies especially to sensitive individuals in the population.

In particular, the BfR has assessed the health risks that might be associated with the consumption of food supplements containing curcumin to which piperine has been added in order to increase the bioavailability of curcumin. However, since the exact composition of such products can vary considerably, a general assessment is not possible from the BfR's point of view. An assessment should always be made on the basis of a specific product with a known composition. Within this context, there is also a fundamental need for research on the toxicity of preparations containing curcumin with improved bioavailability. One aspect here is the question of a possible liver-damaging effect of these products, which cannot yet be adequately answered. Potentially liver-damaging effects have already been observed with curcumin-containing products with improved bioavailability, often through the addition of piperine. In some cases, however, these products also contained other components that could also be (partly) responsible for this.

1 Subject of the Assessment

The food monitoring authorities of the German federal states (‘Laender’) often have to assess food supplements (FS) containing curcumin-enriched extracts from the curcuma rhizome – partly in combination with piperine or piperine-enriched extracts from pepper.

The German Federal Institute for Risk Assessment (BfR) has assessed to what extent the health assessment of curcumin has to be adjusted as piperine, which increases the bioavailability of curcumin, is added to products. In addition, the BfR evaluated possible adverse effects when the acceptable daily intake (ADI) is exceeded.

2 Result

The hazard potential of curcumin[1] has already been assessed in the past by various scientific bodies, in particular within the context of the authorisation of curcumin as a food additive. The European Food Safety Authority (EFSA) derived an ADI (Acceptable Daily Intake) of 3 mg/kg body weight (bw) per day.

The health risks possibly resulting from the intake of piperine have already been assessed within the context of earlier BfR statements (Ziegenhagen *et al.* 2021).For the toxicological assessment of curcumin-enriched products the ADI derived by EFSA should be used as an essential parameter from BfR's point of view. The ADI specifies the quantity of a substance that can be consumed orally on a daily basis over an entire lifetime without a detectable risk to health. Accordingly, the intake of curcumin from all sources should not exceed 3 mg/kg bw and day in the long term. In case of a prolonged exceedance (even slightly), the occurrence of adverse health effects must be considered from a toxicological point of view, especially in sensitive individuals within the population.

In addition, from a toxicological point of view the following aspects should be considered:

- If one takes into account that according to EFSA's estimate – in particular through the use of curcumin as a food additive – average intakes of 0.2-0.4 mg/kg bw and day could be reached in adults, for example, the acceptable intake via FS would have to be adjusted accordingly, since the intake via all sources has to be taken into account for the comparison with the ADI. Even in the case of products with improved bioavailability of curcumin, exceeding the ADI is generally undesirable from a toxicological point of view. However, it applies to these preparations that due to the increase in bioavailability an increase in toxicity must also be considered. The increase in the bioavailability of curcumin by piperine can, however, be very different depending on the dose and the dose ratio between curcumin and piperine. In addition, the bioavailability of curcumin can also be (additionally) increased by other technological processes. Therefore, it cannot be generally stated to what extent the ADI should be adjusted downwards for combination preparations. In the view of the BfR, it should therefore be examined in each individual case whether the ADI derived can ensure a sufficient level of protection or whether the ADI should be adjusted downwards due to a significant increase in bioavailability. This depends on the exact composition of the respective product as well as the manufacturing conditions and the formulation.

[1] In this opinion, the term curcumin is generally used for curcumin-enriched extracts that are known or at least assumed to have a curcuminoid content of at least 90% and are largely comparable to the food additive E100.

- In addition to the endpoint used for deriving the ADI, recent case reports provide indications of potentially liver-damaging effects of preparations containing curcumin. These effects were mostly observed in preparations with improved bioavailability, often through the addition of piperine. In some cases, however, the preparations also contained other components that could also be (partly) responsible for the observed effects. While most cases were observed at intake levels of curcumin above the ADI, according to current knowledge some cases also seem to have occurred at lower doses. In some case reports, a causal relationship between the intake of the products and the observed effects was considered likely. However, no causal relationship between the intake of curcumin and the observed effects can be deduced from the overall available data. A conclusive assessment of the relevance of these reports is therefore not possible on this data basis.

From the BfR's point of view, there is a need for further research on the toxicity of preparations containing curcumin with improved bioavailability – also with regard to the potential hepatotoxicity of these preparations. Within this context, the manufacturers, among others, are responsible for testing the safety of their products by appropriate investigations.

3 Rationale

3.1 Risk assessment

3.1.1 Agent

Curcuminoids are plant constituents found in the rhizomes of various turmeric plants, such as *Curcuma longa* L. and *Curcuma xanthorrhiza* Roxb. The curcuma rootstock contains about 1-5% curcuminoids, with the chemically defined substance curcumin being the main component (Hänsel & Sticher 2007). According to a review by Ahmed & Gilani, the substance curcumin makes up the main part with approx. 75-80%, while the other curcuminoids demethoxycurcumin (DMC, approx. 15-20%) and bisdemethoxycurcumin (BDMC, 3-5%) make up much smaller proportions (Ahmed & Gilani 2014). Curcumin is the chemically defined compound (E,E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. In addition, the ground curcuma rhizome and extracts or extract fractions produced from it are also sometimes referred to as curcumin (Gemeinsame Expertenkommission 2020). In addition, the term curcumin designates the food colouring E100 authorised under Regulation (EC) No. 1333/2008, which is a purified extract from the rhizome of *Curcuma longa*. According to Regulation (EU) 231/2012, the authorised additive must meet certain specifications, including a curcuminoid content of 90%.

The curcumin-enriched extracts used in FS can differ significantly in their exact composition, e.g. due to different manufacturing processes. For the purpose of generalisation, the present statement is based on the simplified assumption that the extracts used in FS are in principle comparable to the extract used as a food additive – i.e. it is a mixture of the above-mentioned curcuminoids with a curcuminoid content of at least 90%. For the sake of simplicity, the term curcumin will be used in the following to refer to a corresponding curcuminoid-enriched extract.

Piperine is a natural ingredient, especially from *Piper nigrum* (black pepper) (Hänsel & Sticher 2007).

3.1.2 Hazard characterisation

3.1.2.1 Curcumin

The hazard potential of curcumin has already been assessed in the past by various scientific bodies, especially within the context of authorisation as a food additive.

Animal data

In a 2004 assessment of the *Joint FAO/WHO Expert Committee on Food Additives* (JECFA), reduced body weight gain in the F2 generation in a two-generation feeding study in rats (Ganiger *et al.* 2007) was considered the most sensitive adverse endpoint. The effects were observed in the highest dose group (corresponding to 850-1100 mg/kg body weight (bw) per day). The middle dose group tested (250-320 mg/kg bw and day) was identified as the "NOEL" (*No Observed Effect Level*). Applying a factor of 100, JECFA derived an ADI (*Acceptable Daily Intake*) of 0-3 mg/kg bw and day (JECFA 2004). The ADI specifies the quantity of a substance that can be consumed orally on a daily basis over an entire lifetime without a detectable risk to health.

The European Food Safety Authority (EFSA) agreed with the conclusions of JECFA in its 2010 re-evaluation of the food additive E100 "curcumin" and confirmed the ADI of 3 mg/kg bw and day based on the same study data (EFSA 2010). A more recent assessment by EFSA in 2020 within the context of the evaluation of curcuma extracts as a feed additive also confirmed the NOEL of 250-320 mg/kg bw for curcumin-enriched extracts based on the above-mentioned study data (EFSA 2020).

Observations in human clinical intervention studies

The available human data paint a contradictory picture. While case reports have described liver-damaging effects that seem to be associated with the intake of curcumin-containing preparations (see section "Case reports"), at most mild adverse effects – e.g. gastrointestinal complaints – were observed in clinical studies in which curcumin was taken in high doses of several grams per subject and day over a period of several months (EFSA 2010; EFSA 2020; Gemeinsame Expertenkommission 2020). According to an evaluation by Lukefahr *et al.* (2018), changes in liver function tests (e.g. transaminases) also occurred in clinical intervention studies with an incidence of 5% (Lukefahr *et al.* 2018). It has been postulated that the observed liver-damaging effects may be an idiosyncratic effect, where there is no clear relationship between dose and effect size (Lukefahr *et al.* 2018; Lombardi *et al.* 2020). An idiosyncratic effect describes the usually innate hypersensitivity to certain substances. However, the indications of a possible liver-damaging potential observed in the clinical studies are to be regarded as not very reliable due to the design of the studies and the low incidence.

Case Reports

The suspected cases of possible liver-damaging effects were predominantly observed after ingestion of preparations with improved bioavailability. There are individual reports of suspected cases from several countries (including the USA and Australia) as well as reports of several suspected cases that occurred in Italy and were recorded via the phytovigilance system set up there (Lombardi *et al.* 2020; Menniti-Ippolito *et al.* 2020).

The work of Menniti-Ippolito *et al.* (2020) describes a case series with a total of 28 suspected cases of acute hepatitis in Italy that were observed in connection with the intake of products containing curcumin (Menniti-Ippolito *et al.* 2020). The median age of the affected persons

was 55 years (range: 27-71). Predominantly women were affected. As a rule, the products were combination preparations containing not only curcumin, usually in high doses, but also other herbal ingredients, often piperine or combinations of different herbal ingredients. Only for a few of the reported cases it is known that no other medicinal products were taken, while in the majority of cases either other medicinal products were also taken or no information was available in this respect. The duration of intake until the onset of symptoms ranged from 8 days to 8 months. For 18 suspected cases, the curcumin intake could be estimated. It ranged between 40 and 1425 mg per day – more precise data related to body weight cannot be taken from this study. In two thirds of the reported suspected cases, however, the intake was about 1.6 to 7 times higher than the ADI, according to the authors.

A paper by Lombardi *et al*. (2020) describes seven suspected cases that occurred in Tuscany. In four of the seven suspected cases, the preparations also contained piperine in addition to curcumin, and in some cases other herbal ingredients were also present. In these suspected cases, the estimated daily intake of curcumin was between 250 and 1812.5 mg, taken over a period of between 2 and 8 weeks. In the suspected case with the lowest daily intake, the body weight of the patient was also given. The ingested dose of 250 mg at a body weight of 60 kg thus corresponds to about 4 mg/kg bw and is thus just above the ADI for curcumin. However, in addition to curcumin, this combination preparation also contained *Boswellia* extract and a red algae preparation. In addition to the described suspected cases from the Italian phytovigilance system, the work of Lombardi *et al*. summarises 13 case reports with a total of 23 suspected cases from the scientific literature. In these cases, symptoms were observed after an intake period of between 2 weeks and 10 months (Lombardi *et al.* 2020).

In principle, in most of the suspected cases observed, typical clinical symptoms of liver damage (e.g. jaundice, dark discoloured urine) were frequently registered in addition to an increase in liver enzymes. Liver biopsies taken in individual suspected cases led to the diagnosis of acute hepatitis (Lombardi *et al.* 2020; Menniti-Ippolito *et al.* 2020). The doses taken are only documented in some of the cases. A clear dose-effect relationship cannot be deduced from the case reports.

In most of the suspected cases described, the symptoms disappeared after discontinuation of the curcumin-containing products. In one case, a worsening was observed after "re-challenge" with the product, which regressed again after discontinuation. In some studies, a causal relationship between the intake of the products and the occurrence of the complaints was considered possible or probable (Lombardi *et al.* 2020; Menniti-Ippolito *et al.* 2020). However, the exact cause remains unknown. Besides the curcumin contained in the products, other factors could also be (jointly) responsible for the hepatotoxic effects. Since most of the affected persons have also taken medicinal products (sometimes several), interactions between curcumin and/or piperine and the respective medicinal products could also have led to or contributed to the liver-damaging effect. The other herbal ingredients contained in some preparations could also be (partly) responsible for the observed effects. In addition, preparations containing only curcuma extracts may have different compositions due to different production methods and may also contain other ingredients of the curcuma root in different compositions in addition to curcumin.

Overall, the reports of suspected cases provide first indications that taking preparations containing curcumin – especially preparations with improved bioavailability – could lead to liver-damaging effects. These were mostly observed at intake levels above the ADI, but may occur in individual cases even at lower doses, possibly due to the improved bioavailability of the respective preparations. A conclusive assessment of the relevance of these reports is therefore not possible on this data basis.

3.1.2.2 Influence of piperine on the bioavailability of curcumin

The natural substance piperine has its own toxicological relevance. The BfR had already assessed the possible health risks from the intake of piperine within the context of earlier statements (Ziegenhagen *et al.* 2021). Within its assessments, the BfR came to the conclusion that a daily intake of 2 mg per person and day (in the form of isolated or enriched piperine as a bolus) should not be exceeded in adults with a body weight of 70 kg. In addition, the addition of piperine, for example in the form of piperine-enriched extracts from pepper, can also lead to an increase in the bioavailability of curcumin. The present statement therefore addresses the influence of piperine on the risks of curcumin by increasing its bioavailability. Questions as to whether the effects described for piperine (change in bioavailability of drugs or substances other than curcumin, maternal and paternal reproductive toxicity effects) can be influenced by a combination of piperine with curcumin are not the subject of this assessment.

The influence of piperine on the bioavailability of curcumin was investigated, among others, in a work by Shoba *et al*. In this study, both rats and human volunteers received either curcumin alone (rats: 2 g curcumin/kg bw; volunteers: 2 g curcumin/volunteer) or curcumin in combination with piperine (rat: 2 g curcumin/kg bw + 20 mg piperine/kg bw; volunteers: 2 g curcumin/volunteer + 20 mg piperine/volunteer). The concomitant administration of piperine increased the bioavailability of curcumin in the rats by a factor of about 1.5, whereas in the volunteers the bioavailability increased by a factor of about 20 with concomitant intake of piperine. The different increase in rats and humans could be due to the significantly different dosage in relation to body weight (Shoba *et al.* 1998). In a study by Zeng *et al*., the influence of piperine on the bioavailability of curcumin was investigated in rats. With simultaneous application of 200 mg curcumin/kg bw in combination with different doses of piperine (2-200 mg/kg bw), an increase in bioavailability by a factor of 1.2 to 1.7 was observed, depending on the dose of piperine (Zeng *et al.* 2017). In a paper by Suresh and Srinivasan, no increase in curcumin bioavailability was observed when 500 mg curcumin/kg bw was co-administered with 20 mg piperine/kg bw to rats compared to curcumin alone (Suresh & Srinivasan 2010). In another human intervention study, in which the subjects received either 2 g curcumin/volunteer or 2 g curcumin/volunteer plus 5 mg piperine/volunteer, only an increase in bioavailability by a factor of about two was observed, in contrast to the study by Shoba *et al*. (1998) (Anand *et al.* 2007). It can thus be assumed that the extent of the bioavailability increase of curcumin through simultaneous intake of piperine can be subject to significant fluctuations. It should also be noted that other technological measures (e.g. nanonised curcumin, micellar formulations) can also significantly increase the bioavailability of curcumin. For example, it seems possible to increase the bioavailability of curcumin by a factor of more than 100 by using micellar formulations (Gemeinsame Expertenkommission 2020). Corresponding processes are also partly used in combination. For example, nanoemulsions of curcumin and piperine are used. This combination seems to increase the bioavailability of curcumin significantly more than the addition of piperine alone (Liu *et al.* 2020).

It is therefore not possible to generalise whether and to what extent the addition of piperine to a particular product increases the bioavailability of curcumin. Since other technological factors in addition to the addition of piperine can also influence the bioavailability of curcumin, the influence can only be assessed in the individual case for a specific product. In principle, an increase in toxicity must be taken into account due to the higher systemic bioavailability.

3.1.3 Exposure

Within the framework of this statement, two expert opinions of food monitoring authorities of the German federal states ('Laender') were submitted as examples. According to the declaration, the products assessed are FS in both cases. The declaration of the first product indicated a curcumin content of 646 mg per daily dose and a piperine content of 10 mg per daily dose. The food monitoring authority determined a curcumin content (analytically determined as the total content of the three main curcuminoids of the curcuma root: Curcumin, DMC and BDMC), which corresponds to a daily dose of 583 mg when taking into account the declared recommendation on consumption. The determined piperine content would lead to a daily intake of 10.3 mg. For a 70 kg person this would correspond to a daily intake of about 8.3 mg curcumin/kg bw and 0.15 mg piperine/kg bw. According to the expert opinion, the second product assessed would lead to an intake of at least 428 mg curcumin and 9.6 mg piperine at the recommended intake level, which corresponds to a daily dose of 6.1 mg curcumin/kg bw and 0.14 mg piperine/kg bw assuming a body weight of 70 kg.

The curcumin and piperine contents of other products marketed as FS may differ. The BfR does not have representative data on this.

With regard to exposure, it should also be considered that curcumin can also be ingested via other foodstuffs. On the one hand, curcumin can be ingested via spices containing curcuma rhizome. On the other hand, exposure results from the use of curcumin as a food additive. EFSA carried out an exposure assessment for the food additive E100 in 2014. The exposure estimation was not based on real occurrence data, but on use levels of the additive as submitted by industry. In addition, natural sources were also taken into account. However, these had no further influence on the estimated intake levels. EFSA concluded that, via the use of E100, mean intakes of 0.4-2.0 mg/kg bw in infants, 0.6-1.6 mg/kg bw in children, 0.2-0.9 mg/kg bw in adolescents, 0.2-0.6 mg/kg bw in adults and 0.1-0.4 mg/kg bw in the elderly (> 65 years) and maximum intakes of 1.4-3.3 mg/kg bw in infants, 1.2-3.4 mg/kg bw in children, 0.7-2.3 mg/kg bw in adolescents, 0.4-1.5 mg/kg bw in adults and 0.3-0.9 mg/kg bw in the elderly (> 65 years) could be reached (EFSA 2014).

3.1.4 Risk characterisation

In the toxicological assessment of curcumin-enriched products, the ADI of 3 mg/kg bw and day derived by EFSA should be used as an essential parameter.

Curcumin-enriched products

According to the EFSA estimate, the use of E100 can already lead to mean intakes of 0.2-0.9 mg/kg bw in adolescents, 0.2-0.6 mg/kg bw in adults and 0.1-0.4 mg/kg bw in the elderly (> 65 years) and maximum intakes of 0.7-2.3 mg/kg bw in adolescents, 0.4-1.5 mg/kg bw in adults and 0.3-0.9 mg/kg bw in the elderly (> 65 years) (EFSA 2014). The first product described above had a curcumin content of 583 mg per recommended daily dose and a piperine content of 10.3 mg per recommended daily dose. For a 70 kg person, this would correspond to an additional daily dose of about 8.3 mg curcumin/kg bw and 0.15 mg piperine/kg bw. With the second product, at least 428 mg curcumin as well as 9.6 mg piperine would be ingested with the recommended intake according to the expert opinion, which corresponds to an additional daily dose of 6.1 mg curcumin/kg bw and 0.14 mg piperine/kg bw assuming a body weight of 70 kg. The ADI of 3 mg/kg bw and day for curcumin derived by EFSA would thus be clearly exceeded. In case of a prolonged exceedance (even slightly), the occurrence of adverse health effects must be considered from a toxicological point of view, especially in sensitive individuals within the population.

The intake of curcumin via all sources should therefore not exceed 3 mg/kg bw and day in the long term. The intake via FS would have to be adjusted accordingly.

Curcumin-enriched products with improved bioavailability

The bioavailability of perorally taken curcumin is low. On the one hand, this is due to the poor absorption via the gastrointestinal tract; on the other hand, the absorbed amount is subject to a pronounced metabolisation in the liver and in the intestine. Against this background, preparation have been developed for some time that are intended to increase the bioavailability after peroral intake. One possibility is the addition of piperine, for example in the form of extracts from pepper (Gemeinsame Expertenkommission 2020).

Even for such curcumin-enriched products with improved bioavailability – e.g. through the addition of piperine – a total daily intake of 3 mg curcumin/kg bw should not be exceeded from a toxicological point of view.

However, due to the increased absorption of curcumin in the gastrointestinal tract and/or a reduced metabolisation, a higher systemic bioavailability and thus in principle an increase in toxicity must be considered for these preparations. For this reason, the existing ADI for such products is not very conservative and may not ensure a sufficient level of protection for consumers.

The increase in the bioavailability of curcumin by piperine can be very different, presumably depending on the dose as well as the dose ratio between curcumin and piperine. In addition, the bioavailability of curcumin can also be (additionally) increased by other technological processes. Therefore, it cannot be generally stated to what extent the existing ADI for curcumin should be adjusted downwards for combination preparations. Such a statement could at best be made for a single product for which the increase in bioavailability is known.

Health risks resulting from a prolonged exceedance of the ADI

The derivation of the ADI for curcumin was based on scientific data on the toxicity of the substance. In a first step, the hazard potential was examined on the basis of toxicological studies and the most sensitive toxicologically relevant endpoint was identified by characterising the dose-response relationship (reduced body weight gain in the F2 generation in a two-generation feeding study in rats (JECFA 2004; EFSA 2010; EFSA 2020). The lowest dose level tested at which this adverse effect occurred (LOAEL) was 850-1100 mg/kg bw per day. The highest dose tested at which no adverse effect was observed in relation to this endpoint (NO(A)EL) was 250-320 mg/kg bw and day, which was about a factor of 3 below the LOAEL. However, it should be noted that at a dose in the range of the NOAEL, no adverse effect can be observed due to the statistical power of a method. However, studies have shown that behind a NOAEL there can already be a small effect strength (on statistical average around 5% for continuous effects) (EFSA 2017), so that from a toxicological point of view the complete absence of undesirable effects must not be assumed at this dose.

In a further step, using the NOAEL as a reference point and applying an extrapolation factor, the ADI was derived. The extrapolation factor is sometimes erroneously called the "safety factor". However, this term is misleading, as this factor does not usually represent a safety margin, but rather an extrapolation to account for the different sensitivities of humans and rats, as well as the different sensitivities within the human population.

While a dose up to the ADI can be orally ingested daily over the entire lifetime without any detectable health risk, from a toxicological point of view, an increase in the probability of the occurrence of adverse health effects must be expected for any longer-term exceedance. It

should be noted that such an assessment is not focussing on the individual but at the population as a whole. In this respect, the occurrence of adverse health effects must be considered from a toxicological point of view in the case of a prolonged exceedance, especially in sensitive individuals within the population.

In addition to the endpoint used for deriving the ADI, recent reports on suspected cases provide indications of possible liver-damaging effects of preparations containing curcumin. These effects were mostly observed in preparations with improved bioavailability, often through the addition of piperine. While most cases were observed at intake levels above the ADI for curcumin, according to current knowledge some cases also seem to have occurred at lower doses. A conclusive assessment of the relevance of these reports is therefore not possible on this data basis.

3.1.5 Recommendations for action

In general, the total intake level of curcumin should not exceed the ADI derived by EFSA, as the occurrence of adverse health effects must be considered from a toxicological point of view in case of a prolonged (even minor) exceedance, especially in sensitive individuals within the population, .

Even in the case of products with improved bioavailability, exceeding the ADI is generally undesirable from a toxicological point of view – but in the BfR's view, it should also be examined in the individual case whether the derived ADI can ensure a sufficient level of protection or whether the ADI should be adjusted downwards due to a significant increase in bioavailability. This depends on the exact composition of the respective product as well as the manufacturing conditions and the technological formulation.

From the BfR's point of view, there is a need for research on the toxicity of preparations containing curcumin with improved bioavailability – especially with regard to potential hepatotoxicity.

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