Statement on the potential risk to human health of turmeric and curcumin supplements

Introduction

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1. The Food Standards Agency (FSA) has been monitoring incidents of adverse events related to consumption of raw and powdered turmeric and its supplements. In light of these incidents and due to the uncertainties surrounding the composition and possible contamination of these commodities, the Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) has been asked to comment on the risk to human health from turmeric, in particular it’s chemical curcuminoid components, consumed in various forms, which include supplements.

2. Turmeric is the common name for the rhizome (underground stem) of Curcuma longa L (Linnaeus), a perennial herb cultivated in tropical and subtropical regions of the world. India is the largest producer of turmeric, supplying over 90 % of the world’s demand (Olojede et al., 2009). There are approximately 70 varieties of C. longa cultivated in India (Sasikumar, 2005). For centuries, turmeric has been widely used as a powder prepared from the rhizome

for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases (Ammon and Wahl, 1991). This powdered form is also known as turmeric.

3. Many of the purported pharmacological properties of turmeric have been attributed to curcuminoids, particularly curcumin (chemical name: diferuloylmethane). These properties include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities (Alok et al., 2015). Curcumin is a polyphenol compound naturally present within turmeric rhizomes. Its derivatives desmethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are also present within turmeric rhizomes. These compounds are collectively called “curcuminoids”.

4. Due to its claimed health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, in recent years there have been a number of reports of hepatotoxicity linked to the consumption of these supplements.

5. The FSA’s Novel Foods Team consider turmeric food supplements, comprising turmeric oleoresin extract or pure curcumin powder, to be novel, because these products were not significantly used as a food or food ingredient before 15th of May 1997. Therefore, before these products may be placed on the market in the UK or EU as a food or supplement, authorisation, which includes a safety assessment, under the Novel Foods Regulations, is required.

6. Curcumin (E 100) is a dicinnamoylmethane dye authorised as a food additive in the EU. It has been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the Scientific Committee on Food (SCF) and the European Food Safety Authority (EFSA). An Acceptable Daily Intake (ADI) of 0 - 3 mg/kg bw had been established by JECFA in 2004 based on a reproductive toxicity study and this was confirmed in the evaluation by EFSA in 2010 (FAO/WHO, 2004a; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010).

7. It is the intended use of the product that defines whether curcuminoids are a food additive or a novel food. If used as a food additive, then this falls under the food additive legislation. When used as a stand-alone ingredient, rather than as an additive, then it would be novel, and subject to the Novel Foods Regulations.

8. It is estimated that supplement intake potentially leads to exposures that are several times higher than through dietary exposure. Synthetic forms of turmeric

and curcumin, or addition of other chemicals such as piperine to turmeric, are used to potentially increase absorption, thus altering the toxicokinetic (TK) profile. The addition of piperine into turmeric supplements is a very common practice. Because of these differences, the COT, in 2020, questioned the relevance of comparing exposures from supplement intake to health-based guidance values for dietary curcumin. It was decided that it would not be appropriate because synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered TK profiles and increased bioavailability. Thus, the levels determined as of low safety concern in food may not be appropriate for supplements.

9. A known safety issue with curcumin and/or turmeric is contamination. Contamination with heavy metals for example can result either from the production of turmeric on contaminated soil or intentional adulteration with, for example, lead (Pb) chromate. Often lead chromate, a Pb-based colour, is used to enhance the appearance (colour) of turmeric. Other yellow chromate salts such as zinc, sodium, potassium or strontium chromate could also be used as adulterants. As a result, raw or ground turmeric could potentially contain high levels of Pb or other metals.

10. Turmeric powder can be intentionally or unintentionally adulterated with chemical dyes or powders of other species of Curcuma, which may be more toxic. For example, the powder of Curcuma zedoaria, a common adulterant in turmeric powder, is potentially toxic; the high-protein flour of C. zedoaria caused 100 % mortality within 6 days when given daily at 320 g/kg diet to 5 week-old rats. The cause of death was unclear (Latif et al., 1979). Furthermore, in supplements, there have been a number of reported cases that involved adulteration with nimesulide, a nonsteroidal anti-inflammatory drug (NSAID) known to cause liver problems.

11. Based on Grand Views Research business intelligence report, the global curcumin market size was approximately $58 million in 2020 and is forecast to progress at a global Compound Annual Growth Rate of 16.1% during the forecast period (2020-2028). Europe is the second biggest market and projected to have the fastest estimated compound annual growth rate of 16.7% between 2020-2028. Regarding market shares, pharmaceutical applications are dominating the curcumin market by revenue and are estimated to have an approximate 50% market share. Food applications were projected to grow by 16% by 2028 (Grand Views Research, 2022).

12. Curcuminoid supplements are generally sold as a capsule containing turmeric powder or a turmeric extract, often containing the adjuvant compound

piperine. Based on a review of the current curcumin supplement market by FSA risk assessors, counting ‘novel’ supplement products as an approximate percentage of all products on sale from major high street retailers, supermarkets and one major online retailer, the proportion of supplements with ‘novel’ micro or nano formulations of curcumin came to approximately 10% of the market. This is with a high degree of uncertainty and it is not known how popular these products are, i.e. how well they sell compared to the standard supplements. From these novel supplements on the market the largest proportion of products were colloidal suspensions, with the use of micelles (e.g., surfactant phospholipids) to deliver the curcuminoids. Many of these products claim that this increased the bioavailability of the curcuminoids. Supplements containing synthetic curcuminoids were rare, developed potentially for pharmacotherapy (e.g., cancer treatment (He et al., 2018)) rather than general health use.

13. In Stohs et al., (2020) review of modified forms of curcumin supplement products it states ‘micelles, liposomes, phospholipid complexes, microemulsions, nano-emulsions, emulsions, solid lipid nanoparticles, nanostructured lipid carriers, biopolymer nanoparticles and microgels’ offer the greatest potential for delivery systems to increase bioavailability. The mechanism is through ‘enhancing small intestine permeation, preventing possible degradation in the microenvironment, increasing plasma half-life and enhancing curcumin efficacy’. (Stohs et al., 2020).

14. This statement summarises the discussions and conclusions of the Committee to date regarding turmeric consumption in food and consumption as ‘conventional’ supplements, i.e., as a curcuminoid/oleoresin extract with or without the adjuvant compound piperine.

Supplements and reported hepatotoxicity

15. Between December 2018 and 20th July 2019, a total of 21 individual cases of acute cholestatic hepatitis “likely to be linked to the consumption of food supplements based on curcumin and piperine” were reported on Italian territory. A total of 18 different turmeric supplements have been associated with this hepatitis outbreak, one of which (“Curcuma Liposomal & black pepper” by Nutrimea) was recalled by Belgium’s Federal Agency for Food Chain Safety (AFSCA) (Chu, W, 2019).

16. Whilst the AFSCA stated that “the exact source of contamination had not yet been established”, an update from Italy’s National Institute of Health indicated that “the interdisciplinary group, section for dietetics and nutrition of

the Technical Committee for animal nutrition and health concluded that, to date, the causes are likely to be related to individual susceptibility, pre-existing alterations, latent hepato-biliary function or even the use of drugs". The Institute did not believe the hepatitis was linked to contamination with heavy metals such as Pb. The Institute adopted a warning for the labelling of the supplements in question (to take effect from 31st December 2019), advising against their use by subjects with altered hepato-biliary function, and recommending medical advice when other medications are being taken. The Institute added that for turmeric powder, which was implicated in one hepatitis case, no particular recommendations were needed, especially considering its history of consumption as a food.

17. As reported by Daniells (2022), Italy's Ministry of Health updated its advice regarding labelling of any products derived from C. longa due to turmeric's potential hepatotoxicity and is continuing to record adverse effects in the Italian population. All products must now state 'In case of liver, biliary or calculosis abnormalities in the biliary tract, the use of this product is not recommended. Do not use during pregnancy and lactation. Do not use for prolonged periods without consulting your doctor. If you are taking medications, it is advisable to hear the opinion of the doctor.'

18. The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) report that their 'nutrivigilance scheme" has received over 100 reports of adverse effects, including 15 reports of hepatitis, potentially related to the consumption of food supplements containing turmeric or curcumin.' This has led the French agency to provide a recent opinion, in June 2022, on turmeric safety (ANSES, 2022).