TOX/2022/68

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Second draft statement on the potential risk to human health of turmeric and curcumin supplements

Introduction

1. The Food Standards Agency (FSA) has been monitoring incidents 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 and its active secondary metabolites curcuminoids in their various forms which include supplements.

2. A discussion paper (TOX/2019/52) was presented to the Committee on 17th September 2019 providing information on the safety of curcumin in supplements and historical turmeric contamination issues, particularly in relation to lead.

3. Two draft statements were presented to the Committee, on 3rd December 2019 and 10th March 2020 which summarised the exposure to raw and powdered turmeric both in the diet and as used in higher quantities for their purported health benefits. The draft statements also covered potential contamination of curcumin and turmeric, which has been associated with adverse health effects in the past.

4. From the COT meeting of 17th September 2019, it was concluded by members that given past reported contamination issues with turmeric

supplements, there would be value in commissioning a chemical analysis of turmeric supplements available on the UK market.

5. A survey of 30 products was undertaken by Fera Science Ltd in Summer 2021. All samples were analysed for the curcuminoids: curcumin, bisdemethoxycurcumin (BDMC) and demethoxycurcumin (DMC) as well as the black pepper derived alkaloid, piperine; and a comprehensive analysis of 69 trace elements which included the heavy metals lead (Pb), mercury (Hg), arsenic (As) and cadmium (Cd). These results were presented in a discussion paper to COT on 29th March 2022 (TOX/2022/19).

6. Since the recent 2021 Fera survey, the FSA have commissioned a further 70 turmeric spice powder analyses for Pb. These were included as part of the annual FSA retail chemical safety (results to be published in early 2023) and imported food surveillance programs (currently no plans to publish these data).

7. In July 2022 a discussion paper was discussed by COT which covered a review of recent literature on bioavailability impact / pharmacokinetics (PK) with adjuvant compounds delivered in supplements with curcuminoids and an updated review of curcuminoid safety when these supplements are taken as a repeat dose over time. The discussion paper in July 2022 also covered a market ‘snapshot’ of ‘novel’ supplements, i.e., synthetic curcuminoids or curcuminoids within micro or nanoparticles for marketing claims of ‘greater absorption’.

8. From the discussion of July 2022 members highlighted that some of the other ‘novel’ supplement types such as micellar nano and micro formulations should be looked at in further detail, regarding their pharmacokinetics and therefore their impact on the active chemicals (e.g., curcuminoids) bioavailability. It has been decided that this will form a new discussion paper in the future as its own topic.

9. This statement provided as Annex A summarises the discussions and conclusions of the Committee from 2019 to date regarding turmeric in food and supplement consumption as ‘conventional’ supplements, i.e., as a curcuminoid / oleoresin extract with or without the adjuvant compound piperine.

10. This statement also includes extra detail on the adulteration of turmeric powders by other Curcuma species, azo dyes and further assessment of trace element data reported after the 30-product survey discussed in the COT meeting of March 2022.

11. This statement references the opinion from the recently published report on ‘Adverse effects associated with the consumption of food supplements containing turmeric’ by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). At this moment in time only the headline conclusions can be referenced as the full report is currently only available in French. An update by the Italian health authorities on the topic is also included.

12. This is the second draft statement which contains suggested changes and wording corrections after recent consideration of the first draft statement by the committee in October 2022. Wording changes are primarily relating to the potential idiosyncratic effect and an updated description of the recently published DIGIN study. This version also contains corrections from the Chair’s comments received after the COT meeting. All changes in this version compared to the first draft statement are highlighted for members information.

Questions for the Committee

13. The Committee are asked to consider:

a) Does the Committee have any comments on the structure or content of the second draft Statement?

TOX/2022/68/Annex A

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Second draft statement on the potential risk to human health of turmeric and curcumin supplements

Introduction

1. The Food Standards Agency (FSA) has been monitoring incidents 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 and it's active secondary metabolites curcuminoids in their 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). In this powdered form it 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 purported 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 of turmeric oleoresin extract or pure curcumin powder, to be novel. 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 Food Regulation, 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 if 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 instead of as an additive then it would be novel, and subject to the novel food regulations.

8. It is estimated that supplement intake potentially leads to exposures that are several magnitudes higher than through dietary exposure. Furthermore, 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 is a result of either the production of turmeric on contaminated soil or intentional adulteration with, for example, lead chromate. Often lead (Pb) chromate, a Pb-based colour, is used to enhance the appearance 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 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 (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 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 towards progression 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 being 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 draft 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 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 dietetics, and 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 a 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 Danielles (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. ANSES (the French Agency for Food, Environmental and Occupational Health & Safety) 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).

Toxicokinetics

19. In both humans and animals, curcumin when consumed as a food additive has been shown to have low oral bioavailability.

20. Approximately 75% of the administered dose was excreted unchanged in the faeces with negligible amounts appearing in the urine following oral administration of 1 g/kg bw of curcumin in rats (Wahlström and Blennow, 1978). The oral bioavailability of curcumin in the rat was < 1%, by comparing the Area Under the Curve (AUC) after oral and intravenous administration (Yang et al., 2007). Oral bioavailability is similarly low in humans, due to poor absorption and extensive first-pass metabolism in the intestine and liver (Ireson et al., 2002). Curcuminoids are susceptible to phase II metabolism in the gastrointestinal tract and / or the liver, with glucuronides identified as being the dominant metabolites (Wang et al., 2019).

21. Furthermore, it is also reported that the low bioavailability of curcuminoids is due to low membrane transfer and hence low absorption. The

underlying mechanisms are an active efflux by P-glycoprotein (pGP) and inter-molecular interactions.(Heger et al., 2014; Jamwal, 2018; Ji et al., 2016). Curcumin is reported as acting as an inhibitor of pGP, both in function and expression (at the protein and mRNA level) (Lopes-Rodrigues et al., 2016). Overall, the low bioavailability of curcuminoids can be attributed to a number of factors including rapid metabolism, efflux transport and low cellular transfer.

22. Numerous studies in animals have evaluated the level of curcumin after administration and found that no curcumin, or only low levels, were detected in serum or tissue (Ravindranath and Chandrasekhara, 1981; Shen and Ji, 2012).

23. In supplements it is common practice to alter the curcumin product to change its metabolism and enhance its bioavailability, by addressing the metabolism using metabolism inhibitors, membrane permeability or both. This can be achieved with methods such as the use of liposomal curcumin encapsulation, nanoparticle dispersion (as part of a nano or microemulsion (Liu et al., 2020)), the use of micelles, i.e. a curcumin phospholipid complex and / or the use of synthetic structural analogues of curcumin that are water soluble.

24. The use of adjuvants is currently the most widely adopted modification in turmeric supplements. For example, piperine is the most widely used adjuvant. It is the major active ingredient in black pepper, and is a known inhibitor of glucuronidation in the liver and intestine (Di et al., 2015). Hence, piperine may provide a corresponding decrease in the metabolism of curcuminoids. Furthermore, it is reported that piperine may interfere with efflux mechanisms by, for example pGP, in the epithelial cells that expel compounds back into the intestine for excretion (Chen et al., 2020). This results in a change of permeation properties of the intestine (Khajuria et al., 2002) and therefore compounds with low bioavailability due to lower membrane crossing, such as curcuminoids, can subsequently be better absorbed. Piperine may also directly increase the intestinal absorptive surface

due to the induction of the synthesis of proteins associated with cytoskeletal function of the epithelial cells of the intestine (Khajuria et al., 2002). However, the relevance of the findings from this paper are highly questionable because of the use of high doses and small changes reported.

25. In an in vitro study using Caco-2 cells Wang et al., (2019) showed that the absorption of curcumin was significantly increased (by approximately 2.5-fold) ($p < 0.01$), when cells were exposed alongside piperine, suggesting piperine could promote the intestinal absorption of curcumin. However, this study used a co-amorphous formulation that may not be representative of 'real world' use.

26. Piperine has been shown to increase the bioavailability of curcumin by up to 154% in rats and up to 2,000% in a human study (Shoba et al., 1998). In this study, piperine was administered at 20 mg/kg concomitantly with curcumin at 2 g/kg to Wistar rats (single dose), and at 20 mg/kg in humans with curcumin at 2 g total (also a single dose). The 'curcumin only' control group returned results < LOD for curcumin in serum and the value of a 2000% increase was the AUC measurement. It is not clear from this study what assumptions were made regarding the non-detects in serum.

27. There is evidence in the recent literature that shows piperine may have less of an effect on bioavailability as an adjuvant compound than previously reported. Fanca-Berthon et al., (2021) undertook a study using a cohort of 30 human volunteers assessing several different curcumin supplement delivery mechanisms. The piperine-curcuminoid dose combination included approximately 15 mg of piperine with 1,500 mg of curcuminoids. The study monitored blood plasma concentrations over a 24-hour period after a single dose and included metabolites of curcuminoids as well as the parent compounds curcumin, BDMC and DMC to provide a 'total curcuminoids' blood plasma concentration. The piperine-curcuminoid combination did not show any significant differences to the curcuminoid only

standard extract, contrary to the Shoba et al., (1998) human study (Fança-Berthon et al., 2021).

28. Fanca-Berthon et al., (2021) gave several potential reasons for the differences in these findings from the Shoba et al., (1998) study:

- The Shoba study had only 8 study participants compared to 30 in the Fanca-Berthon et al. study.
- Shoba et al. studied a shorter kinetic duration, sampling for only 6 hours compared to 24 hours in the Fanca-Berthon study, which found a Tmax of 6 hours for the parent curcuminoid compounds.
- Shoba et al. only measured the single compound curcumin, compared to the metabolites and other related curcuminoids analysed in the Fanca-Berthon study and used for their conclusions, which state: 'Based on the individual quantification of 15 curcuminoid metabolites, this study demonstrated that unconjugated curcumin, DMC, and BDMC represented only 1% of the total plasma curcuminoids following oral administration of a variety of turmeric formulations. Curcumin plasma concentration alone only reached a maximum of 18 – 21.5 ng/mL in contrast to >400 ng/mL for all metabolites combined.'

29. There is a lack of any further studies providing direct evidence of piperine enhancing the bioavailability of curcumin in humans, however there are several examples of piperine being used to aid the bioavailability of other compounds. (Bano et al., 1991; Di et al., 2015; Lambert et al., 2004).

30. No other studies could be found in the literature that reported a negative or 'no effect' of piperine when used as an adjuvant compound to aid the bioavailability of curcuminoids. This may be due to the common drawbacks of assessing the peer reviewed literature for negative or 'no effect' conclusions, i.e. these studies are often unreported (Joober et al., 2012).

31. Based on the in vitro and in vivo studies above, the TK of curcuminoids, taken as a supplement alongside piperine, could be very

different to the kinetics when consumed via conventional dietary exposure as a flavouring. However, based on the evidence available it seems unlikely that any difference in consumers would be marked.

Toxicity

Derivation of a Health Based Guidance Value (further details provided in Annex B)

32. In 1975, the Scientific Committee for Food (SCF) evaluated curcumin. They considered that curcumin (from natural foods) could be classified as a colour, and although an ADI could not be established it was nevertheless acceptable for use in food (SCF, 1975).

33. In 1995, JECFA on the basis of the NOAEL of 220 mg/kg bw/day in the carcinogenicity study of mice and a safety factor of 200, established a temporary ADI of 0 - 1 mg/kg bw for curcumin pending the submission of the results of a reproductive toxicity study (FAO/WHO, 1995).

34. In 2004, JECFA withdrew the temporary ADI and established an ADI for curcumin of 0 - 3 mg/kg bw based on a NOAEL of 250 mg/kg bw/day for significant decreases in the average bodyweights of Wistar rat F2 generation pups in a reproductive toxicity study at 960 – 1100 mg/kg bw/day (FAO/WHO, 2004a).

35. In 2010, based on the study used by JECFA, the EFSA ANS panel concluded that the present database supported an ADI of 3 mg/kg bw/day, also based on significant decreases in the average bodyweights of Wistar rat F2 generation pups (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010). EFSA also reported human studies where volunteers were exposed to relatively high doses of curcumin either via single dose or up to several months. For dose levels up to 12,000 mg/day, only short-term and semi-chronic (sic) adverse effects, such as gastrointestinal

effects, headache and rash were observed, but without a clear dose-relationship.

36. In the meeting of the COT on 10th March 2020 Members questioned the relevance of comparing exposures from supplement intake to the ADI 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 relevant for supplements.

Hepatitis and idiosyncratic drug hepatotoxicity (further details provided in Annex B)

37. Hepatitis is the general term for inflammation of the liver. This has a range of clinical presentations varying in duration, severity and eventual outcome. The initial symptoms of hepatitis are often non-specific but in the later stages of the disease the symptoms reflect impairment of various liver functions. Laboratory evidence of liver cell damage can often be detected in asymptomatic patients but significant impact on the synthetic, metabolic and excretory functions of the liver eventually leads to symptoms such as bruising secondary to lack of clotting factors, encephalopathy caused by failure to convert ammonia to urea, and itching when bile salts are potentially deposited in the skin instead of being eliminated in the bile.

38. In the UK, the most common causes of liver injury are fatty infiltration of the liver or viral infection, but toxicants (including alcohol), genetic storage disease and autoimmune processes can also lead to liver damage. In a proportion of patients, no ready explanation can be found for liver damage however severe. Toxicant-induced hepatitis, usually caused by drugs, is not uncommon and resolves when the relevant chemical exposure ceases. In some cases, however, cellular damage is severe and the outcome can be

fatal. In a few patients severe liver disease may develop, even when the initial response is mild, due to individual susceptibility (idiosyncratic liver disease).

39. Identifying a cause for an episode of hepatitis depends upon a knowledge of the history of exposure to chemicals, drugs or contact with sources of hepatitis infection, together with laboratory investigations. Infection with many of the hepatitc viruses can be identified either by demonstrating an antigenic part of the virus or a specific antibody response to the virus in the blood. Autoimmune disease can be diagnosed from the pattern of antibodies to specific cellular components such as from the mitochondria or nuclei and from the clinical picture of other organ involvement. Damaged liver cells tend to leak enzymes into the blood and some clue as to the site of greatest damage within the liver can be gleaned from the pattern of these enzymes with transaminases, particularly alanine aminotransferase (ALT), being released from damaged parenchymal cells and alkaline phosphatase being released from cells lining the bile ducts.

40. Idiosyncratic drug hepatotoxicity (IDH) occurs in 1/500 to 1/50,000 individuals exposed to a particular drug (the prevalence of idiopathic hepatitis in the community is estimated to be 1/100,000) (Kaplowitz, 2005). IDH has been associated with a variety of pharmaceutical drugs as well as food supplements, notably kava kava. IDH is variable, person specific and occurs for a number of drugs, but also does not occur for many others. Idiosyncratic events are not caused just by the drug itself but by reactions unique to the individual (e.g. due to a genetic predisposition) who is exposed to it (Apica and Lee, 2014). However, without the drug there would be no effect. IDH is generally too rare to be detected in clinical trials, though elevated ALT levels may be an indicator. As a general rule, an ALT level greater than three times the upper level of normal is considered to be a sensitive indicator of liver toxicity (the marker is not completely specific since muscle injury may elevate ALT levels). While this is nearly universally described for idiosyncratic liver toxicants, it is not always predictive of overt idiosyncratic toxicity as many patients with elevated ALT levels do not develop IDH.

41. Two types of IDH can occur. Allergic IDH occurs with a short latency period and involves the adaptive immune system. Symptoms may include fever, rash or eosinophilia. It is not well understood why some individuals have or subsequently develop allergic IDH. However, it is likely due to an individual's genetics, body chemistry at a particular time of life, frequent or multiple drug exposures and/or the presence of an underlying disease. Non-allergic IDH has none of the above features (except genetic predisposition). There can be a long latency period, where there may have been months of normal liver function test results prior to the occurrence of IDH. Symptoms vary depending on the drug but can include, for example, gastrointestinal irritation and vomiting (American Academy of Allergy Asthma & Immunology, 2020).

Curcuminoids and hepatotoxicity

42. Full details of the relevant animal and human studies were provided in the COT discussion paper TOX/2019/52 and summarised in Annex B.

43. In short there are a number of animal and human studies covering acute, sub-chronic and chronic toxicity of curcuminoids. There is no key study but there is a weight of evidence for hepatotoxicity being the critical toxicological endpoint, which the COT previously considered.

44. There is evidence that the hepatotoxicity of curcuminoids has a reversible nature, both in rats (Chavalittumrong et al., 2002) and in human cases, where liver function tests normalised after ceasing consumption of the supplement (Luber et al., 2019; Lukefahr et al., 2018; Suhail et al., 2020).

45. 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 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).

46. A long-term study undertaken by the US Drug-Induced Liver Injury Network (DILIN) between 2004 and 2022 examined the clinical, histologic and human leukocyte antigen (HLA) associations of turmeric related hepatotoxicity in patients. They concluded of the 2,392 recorded drug induced liver injuries, 10 (0.4%) could be attributed to turmeric consumption, occurring between 1 and 4 months of regular intake. No other drug or chemical supplement was implicated in these cases. The authors concluded that liver injury primarily occurs in women using turmeric for arthritis, pain relief and/or general health. Of the 10 cases, five were hospitalised with acute liver failure and 1 of these cases died of their injuries. Of the 10 cases, seven of the turmeric products the patients were regularly consuming were chemically analysed. All 7 contained the adjuvant compound piperine. From HLA sequencing, 7 of the 10 patients were found to carry HLA-B*35:01, a class I HLA allele previously associated with green tea hepatoxicity. Overall, the authors concluded that "Turmeric causes potentially severe liver injury that is typically hepatocellular, with a latency of 1 to 4 months and strong linkage to HLA-B*35:01" (Halegoua-DeMarzio et al., 2022).

47. 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). In their opinion, ANSES advises against 'the consumption of food supplements containing turmeric by people with bile duct disease' and that 'there is a risk of curcumin interacting with certain medications such as anticoagulants, cancer drugs and immunosuppressants.'

48. Pancholi et al., (2021) dispute the potential hepatoxic effects reported in human studies. They state that only a handful of human cases reporting toxic symptoms, out of millions of humans exposed to curcuminoid

supplements daily, is not a significant finding, with those that have symptoms having other personal reasons for these. However, it should be noted that 3 of the authors of the Pancholi et al., (2021) publication are employed by a supplements company which funded the study, with little new evidence provided on the possible idiosyncratic effects of curcuminoids.

Medium to long term safety of curcuminoids

49. Pancholi et al., (2021) present a 90-day safety study in humans taking supplements containing curcuminoids. Twenty healthy human volunteers were given 380 mg of curcuminoids daily (adjuvanted with fenugreek derived galactomannans as a curcumin-galactomannoside complex) for 90 days. Aspartate aminotransferase (AST), ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin were all within a normal range after the 90-day exposure, indicating no liver effects after this time period. Little new evidence was provided on the possible idiosyncratic effects of curcuminoids

50. Gupta, Patchva and Aggarwal, (2012) report that ‘safety, tolerability, and nontoxicity of curcumin at high doses are well established by human clinical trials’. They reference a study providing 8 g of curcuminoids daily to 21 pancreatic cancer patients for between 3 and 14 months alongside their regular chemotherapy treatment. Adverse effects reported, including, for example, neutropenia and fatigue were attributed to the chemotherapy treatment and/or disease progression rather than the curcuminoid supplement (Kanai et al., 2011).

51. In a double-blind, placebo-controlled study by Petracca et al., (2021) 80 multiple sclerosis patients were enrolled onto a trial, 40 of whom received 500 mg of curcumin twice daily for 24 months. Only 53 patients completed the full time period of the trial. No differences in the occurrence of adverse effects were reported in the patient group taking curcumin supplements compared to the controls.

52. Amalraj et al., (2021) describe a double-blind, placebo-controlled study in 30 healthy volunteers (15 volunteers per two groups). The test group were given 500 mg of curcumin daily for 8 weeks. The supplement was provided as an asafoetida (an oleo gum resin) - curcumin complex. No adverse effects were reported in any of the volunteers during the study.

53. There are numerous other similar clinical trials in the literature showing the potential repeat dose safety of curcuminoid consumption at similar or higher concentrations provided in supplements. Examples include trials with no adverse effects reported by Appelboom et al., 2014 (84 mg taken daily over 6 months by 820 patients), Haroyan et al., 2018 (approx. 1 g taken daily over 12 weeks by 133 patients), Nakagawa et al., 2022 (180 mg taken daily for 12 months by 23 patients) and Sterzi et al., 2016 (100 mg taken daily for 8 weeks by 26 patients).

Contamination of raw, ground turmeric and curcumin supplements with lead (Pb)

54. Raw turmeric can be contaminated with Pb as a result of either growth of turmeric on Pb rich soil or intentional adulteration with lead chromate (Cowell et al., 2017). It has been reported that lead chromate, a Pb-based colour, may be used to enhance the appearance of turmeric (Forsyth et al., 2019). As a result, raw or ground turmeric could potentially contain high levels of Pb. Forsyth et al., (2019) found Pb concentrations as high as 1,150 mg/kg in an extensive turmeric survey in Bangladesh.

55. Pb in the body is distributed to the brain, liver, kidney and bones. It is stored in the teeth and bones, where it accumulates over time. Human exposure is usually assessed through the measurement of Pb in blood. Pb in bone is released into blood during pregnancy and becomes a source of exposure in the developing fetus (WHO, 2022).

56. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment of Pb exposure. The respective BMDLs derived from blood Pb levels in µg/L (corresponding dietary intake values in µg/kg bw/d) were: developmental neurotoxicity $BMDL_{01}$, 12 (0.50); increased systolic blood pressure (SBP) $BMDL_{01}$, 36 (1.50); increased prevalence of chronic kidney disease $BMDL_{10}$, 15 (0.63). The Panel highlighted that by protecting children, who are far more sensitive, from the developmental effects of Pb, the general population would also be protected from any adverse effects (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010). In young children, EFSA concluded that a MOE of 10 or greater (for the corresponding dietary intake values) should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ. At lower MOEs, but greater than 1.0, the risk was likely to be low, but not such that it could be dismissed as of no potential concern.

57. After review of the EFSA and JECFA 2011 (FAO/WHO, 2011) evaluations, COT (COT, 2013) agreed that neurodevelopmental effects of Pb represent the most sensitive endpoint, whilst also being protective of the other toxicological end points.

Contamination with other potential adulterants

C.zedoaria

58. Turmeric may be adulterated with other curcuma species such as C. zedoaria., also known as zedoary or white turmeric (Dhakal et al., 2019). This is a plant in the same genus that has lower curcumin content and cost but produces a higher yield.

59. The literature on the toxicity of C. zedoaria is limited. In a subacute toxicity study C. zedoaria caused elevation of liver enzymes at levels of 62.5 mg/kg bw and above in mice (Lakshmi et al., 2011). The essential oil of

C. zedoaria was also found to significantly increase the levels of ALT and ALP at 100 and 200 mg/kg bw/d in pregnant rats treated from Gestation Day (GD) 7 to GD17. The levels of AST were significantly increased at 200 mg/kg bw/d. In the same paper, rat embryos treated ex vivo at doses of 10, 20 and 40 µg/ml with the essential oil exhibited developmental toxicity as observed from changes in yolk sac diameter, crown-rump length, head length, number of somites and score of flexion, heart, fore and hind brain (Zhou et al., 2013). The high-protein flour of C. zedoaria caused 100 % mortality within 6 days when given at 320 g/kg diet to 5 week-old rats (Latif et al., 1979). It has been reported that despite causing central nervous system depression and affecting liver enzymes at high doses, at the levels present in turmeric mixes as well as from traditional use in food C. zedoaria would not be of concern (Bejar Ezra, 2018). However, quantification of the levels present in adulterated turmeric would be needed in order to establish the risk.

Azo dyes

60. The literature reports adulteration of turmeric powders with azo dyes which are prohibited in foods, such as Sudan dye and Metanil yellow (Sasikumar, 2019). These are aromatic compounds containing an azo group (R-N=N-R) and are not permitted as food additives due to their potential carcinogenicity. In their review in 1987, the International Agency for Research on Cancer (IARC) classified the azo dyes Sudan I–IV as Class 3 carcinogens, i.e. had insufficient information to reach a conclusion (Pan et al., 2012).

61. A number of animal studies have shown potential tumour formation given the exposure of different Sudan dyes in food products (Nisa et al., 2016). Tsuda et al., (2000), from an in vivo comet assay using ddY mice, showed that 17 azo compounds were positive for genotoxicity.

62. The German Federal Institute for Risk Assessment (BfR, 2003) concluded that for the Sudan dyes, given their potential genotoxic mechanism of action, a concentration cannot be determined for these chemical

compounds at which a carcinogenic action does not occur (the 'threshold value'). Therefore, the BfR could not propose a tolerable daily intake (TDI) for the Sudan dyes.

63. EFSA (2005) concluded that there are insufficient toxicology data on any of the illegal azo dyes to undertake a full risk assessment. However, EFSA did state that there is enough experimental evidence to conclude that Sudan I is both genotoxic and carcinogenic.

64. Regarding the yellow azo dyes, there is evidence to suggest they may be neurotoxic and hepatotoxic. Nagaraja and Desiraju, (1993) reported that in Wistar rats the administration of Metanil yellow affected the developing and adult brain. 'In the treated rats the amine levels in the hypothalamus, striatum and brain stem were significantly affected, and the changes were not generally reversible even after withdrawal of the dye.'

65. Saxena and Sharma, (2015) describe hepatoxic effects in Swiss albino rats when administering a mixture of the three yellow azo dyes Metanil yellow, Sunset yellow and Tartrazine. 'Significantly increased concentrations of serum total protein, serum albumin, serum ALP and hepatic malondialdehyde and significantly lowered levels of superoxide dismutase, reduced glutathione and catalase in the liver tissue of treated animals were observed when compared with control animals.' Furthermore, in the treated groups infiltration of hepatocytes were observed along with necroscopy and vacuolation.

66. In EFSA's 2005 evaluation on consideration of Metanil yellow the committee stated that there was indication of genotoxic activity however concluded there was 'some indication of tumour promoting activity but probably only through enzyme induction.'

67. In 2017 JECFA evaluated the yellow azo dyes Quinoline Yellow and D&C Yellow No. 10. They concluded that due to their similar chemical structures and manufacturing process that it would be acceptable to take the toxicology data for D&C Yellow No. 10 to support conclusions for Quinoline

Yellow. Considering the two similar long-term studies on D&C Yellow No. 10 in Sprague Dawley rats (Hogan, G.K. and Knezevich, A.L., 1982a, 1982b) a dietary NOAEL of 0.5% (equivalent to 250 mg/kg bw per day), based on effects on body and organ weights was identified. Using this NOAEL and an uncertainty factor of 100, JECFA established an ADI of 0–3 mg/kg bw for Quinoline Yellow (FAO/WHO, 2017).

Exposure assessment

Exposure from food

68. Curcumin powder is authorised for use as a colouring agent in food (E 100), where its purity is specified as “not less than 90 % total colouring matters” (i.e. curcumin, DMC, and BDMC) (EC, 2008). Directive 94/36 states the maximum permitted levels (MPLs) for E 100 in foodstuffs, range from 20 to 500 mg/kg, depending on the food item and beverages (which range from 100 to 200 mg/L) (EC, 1994).

69. A previous discussion paper (TOX/2019/52) addressed dietary exposure using turmeric (curcumin) consumption data from the EFSA ANS 2010 evaluation which used adult data from the UK National Diet and Nutrition Survey (NDNS) 2000 - 2001 and child data from the European (EXPOCHI) project (EFSA ANS, 2010). Further details can be found in Annex B.

70. Dietary curcumin exposure was within the JECFA 2004 ADI of 0 - 3 mg/kg bw (FAO/WHO, 2004a) for both adults and children when using UK NDNS data and taking the mean exposure using both maximum reported occurrence concentrations and maximum permitted levels.

Exposure through turmeric supplements

71. In addition to exposure to curcumin through a normal diet, turmeric supplements can also be taken. These can be bought as ‘over the counter’

supplements or by ‘self-dosing’, through consumption of spices in large quantities. The exposures for curcumin and heavy metals from supplements have been calculated using data from a recent survey by Fera (Fera Science Ltd, 2022) and are described in paragraphs 76 – 82.

72. Curcuminoids can be extracted from ground turmeric powder using organic solvents to create a turmeric oleoresin extract. JECFA lists several solvents permitted for extraction: acetone, methanol, ethanol, and isopropanol (FAO/WHO, 2004b). The European Commission, however, has a different list of permitted solvents: acetone, carbon dioxide, ethyl acetate, dichloromethane, n-butanol, methanol, ethanol, and hexane (EC, 2008). According to JECFA specifications, residual solvent concentrations in turmeric oleoresin intended for use in food are limited to 25 mg/kg for hexane, 30 mg/kg for acetone and 50 mg/kg for ethanol, methanol, and isopropanol (FAO/WHO, 2004b). The extraction methodology used affects the curcuminoid content (37-55 %) (Li, et al., 2011), and the essential oil content (< 25%) (Braga et al., 2003) of the turmeric oleoresin.

73. Turmeric oil extract can be prepared in various ways, for example through the treatment of turmeric powder with steam distillation, supercritical CO_2 extraction (Li et al., 2011), or by evaporating the organic solvent of a crude turmeric oleoresin extract (Funk et al., 2010).

74. Curcumin powder can be obtained through the purification of turmeric oleoresin by crystallisation (Li et al., 2011). However, there can be limited commercial availability of authentic samples of pure curcumin, since its separation from DMC and BDMC can be difficult and time consuming. Thus, commercial “pure” curcumin is, in many cases, a mixture of at least these three curcuminoids (Li et al., 2011). For example, a sample of commercial “pure” curcumin (labelled as 94 % purity) was, after HPLC analysis, found to have approximately 70 % purity (Li et al., 2011). In addition, the composition of a sample of commercial “curcumin” was found to be approximately 71.5 % curcumin, 19.4 % DMC, and 9.1 % BDMC (Pfeiffer et al., 2003).

75. As mentioned earlier in this statement and described in paragraphs 23 - 31, in supplements it is common practice to alter the curcumin product to change its metabolism and enhance its bioavailability, by addressing the metabolism, membrane transfer or both. This can be achieved with methods such as the use of liposomal curcumin, nanoparticle dispersion, the use of curcumin phospholipid complex and the use of structural analogues of curcumin that are water soluble.

Assessment after 2021 sample survey - Curcuminoids

76. Previously, in discussion paper TOX/2019/52, a range of supplement information was used to estimate exposure to curcuminoids. Since this paper was written a sample survey has been commissioned by the FSA and undertaken by Fera Science Ltd in Summer 2021. The final report for this survey can be found on the FSA website (Fera Science Ltd, 2022).

77. Thirty samples were purchased from a variety of sources (online suppliers, large supermarkets and small retailers) and analysed by Fera Science Ltd using mass spectrometry. The samples consisted of supplements (n=15), ground/powdered turmeric (n=10) and fresh turmeric root (n=5). One of the fresh samples arrived dried.

78. All samples were analysed in duplicate for the curcuminoids: curcumin, BDMC and DMC as well as the black pepper derived alkaloid piperine.

79. Of the supplements sampled, 5 had total curcuminoids over 10%, with one at almost 30%, and one at almost 50% absolute concentration. Of the 5 supplements providing concentrations of total curcuminoids on the label all results were within ± 20 % of the stated concentration.

80. From the survey, taking the recommended doses daily according to the supplement's label, exposure levels for a 70 kg adult would range from 0.1 to 7 mg/kg bw/day (mean of 1.7 mg/kg bw/day). Two of the 15 supplement samples would lead to exposures above the dietary ADI of 3 mg/kg bw day. Taking the supplement that provides 7 mg/kg bw/day for a 70 kg adult, would contribute a further approximate 3-fold in exposure to curcuminoids than would be expected from a high dietary exposure (2.6 mg/kg bw/day), highlighted and discussed in Annex B to this statement (Annex B, Table 2.)

81. Ten of the 15 supplements contained detectable concentrations of piperine with 6 of those > 1 %, which could potentially alter the TK of the curcumin compounds consumed within the same supplement. One of the samples containing piperine did not state this on the label. Three of the supplements contained piperine at approximately 10% or higher.

82. From the powder samples analysed, i.e., where turmeric is sold as a spice ingredient, if these samples were to be taken as a supplement rather than a food ingredient, e.g., at a teaspoon (4 g) a day, exposures would all be within the ADI of 0 - 3 mg/kg bw/day.

Assessment after 2021 sample survey - Heavy Metals and other trace elements

83. From the recent survey undertaken by Fera Science Ltd (Fera Science Ltd, 2022) described above, all samples were analysed for 69 trace elements, which included the heavy metals Pb, Hg, As, and Cd.

84. Twenty-nine of the 30 samples tested had heavy metal concentrations of low concern, i.e., below the maximum level (ML) set for supplements by retained EU legislation EC 1881/2006 or below the EU ML set for root spices by the amendment EU 2021/1317 (due to the recent date, this amendment to the EU regulation is not in UK legislation). For supplements, the MLs are 3 mg/kg for Pb, 1 mg/kg for Cd and 0.1 mg/kg for Hg. For root spice powders

the EU ML is 1.5 mg/kg for Pb. Arsenic does not have a ML set for supplements, but all concentrations, bar two samples at 0.45 and 0.29 mg/kg, were below the 0.2 mg/kg ML set for white rice by EU 2015/1006.

85. One sample, a turmeric spice powder, contained a Pb concentration approximately 10 times higher than the majority of other samples analysed, at 2.25 mg/kg. This would be over the amended recent EU ML of 1.5 mg/kg for root spice powders. This sample also had the second highest concentration of chromium (Cr) at 2.11 mg/kg, which may indicate adulteration with lead chromate. If this sample were taken as a supplement at, for example, a teaspoon per day (4g) the total exposure of lead from this source alone would be 0.13 µg/kg bw/day for a 70 kg adult. This is approximately 25% of the estimated dietary exposure of 0.5 µg/kg bw day, equivalent to the $BMDL_{01}$ of 12 µg/L blood Pb concentration, for effects of Pb on developmental neurotoxicity (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010).

86. When the heavy metal results for supplement samples were compared against spice powders and fresh turmeric there were no clear trends or significant differences between the groups (supplements against powder & fresh samples).

87. On evaluation of the other trace elements from the 30 samples, results that differed by greater than the mean plus 2 x the standard deviation and 5 x the mean of that sample type (i.e., fresh, powder or supplement) are summarised in Annex B. If taking the supplements as described on their labels, no estimated exposures for any trace elements would exceed any health-based guidance values (HBGVs), where HBGVs exist.

88. Overall, the trace element profile of each sample was variable, this is explained by:

a) The different geographical sources of the products and therefore the differing background trace element concentrations from the environment the products were derived.

b) The varying chemical nature of the different supplement formulations.

89. Since the recent 2021 Fera survey, the FSA in 2022 have commissioned a further 70 turmeric spice powder sample analyses for Pb. All results were < 0.5 mg/kg and of no health concern.

Exposure of other potential adulterants

C.zedoaria

90. The occurrence data within the literature of adulteration of C. longa with C. zedoaria is extremely limited. Sasikumar et al., (2004) describe 3 samples of turmeric powder bought from an Indian market that were found to contain more of the contaminant C. zedoaria than the expected C. longa. Due to the much lower price and easier availability of the potential adulterant C. zedoaria (Dhanya et al., 2011), adulteration of products appears to be assumed rather than any direct evidence in the available literature from chemical analysis. Sasikumar (2019) describes wild curcuma species as common adulterants of turmeric products.

Azo dyes

91. The occurrence data of Sudan red and Metanil yellow dyes in turmeric powders is primarily from surveys undertaken from Indian and Pakistan spice markets. Dixit, Khanna and Das, (2008) with a sample size of 15 turmeric powders from an Indian market, report concentrations of adulteration with Sudan dyes between 0.09% and 1.2% and Metanil yellow between 0.15% and 0.46%.

92. Dixit et al., (2009) report results for a much larger survey across Indian markets, analysing for Metanil yellow only. This included 100 branded turmeric powders and 612 non branded products. None of the branded products contained the dye, 17% (105 samples) of the non-branded powders contained Metanil yellow ranging in concentration between 0.1% to 0.85%.

93. In other surveys from the literature, from a survey of 9 non-branded products Rao et al., (2021) found two products contained Metanil yellow at approximately 0.1%. Ullah et al., (2022) from a survey of branded and non-branded turmeric powders from Pakistan markets (total sample numbers unknown) found Sudan dyes between 1.5 mg/kg (0.00015 %) and 8,460 mg/kg (0.84 %) in the non-branded samples only.

94. From a recent FSA survey of 30 turmeric spice products (this included 6 non-branded products) in 2022, no illegal dyes were detected. Although this did not include the Sudan red dyes or Metanil yellow.

Risk Characterisation

Curcuminoids

95. As detailed in Annex B, consumption as part of the normal diet (from its use as an additive and spice) would lead to curcumin exposures that are generally within the ADI of 0 - 3 mg/kg bw.

96. There is high uncertainty regarding the risk from the intake of raw and powdered turmeric in high quantities for their purported health benefits. The literature review of human studies within the 2019 COT discussion paper (TOX/2019/52) suggests oral intake of curcuminoids in humans is well tolerated up to doses of 114 mg/kg bw/day, though minor symptoms of nausea or diarrhoea may occur. Longer term clinical studies summarised in this statement suggest that daily consumption of curcuminoids at concentrations at or above those found in supplements result in no adverse effects.

97. With regard to dietary turmeric supplements, a recent 2021 survey shows that a small proportion (2 from 15 samples) of the tested products would lead to high exposure of curcuminoids i.e. exposures at or above the ADI of 0 - 3 mg/kg bw. The COT concluded from previous discussions that this ADI may not be appropriate for supplements. This is because as also shown in the 2021 survey, 10 of the 15 supplements analysed contained piperine which may be formulated to increase its bioavailability from that of natural curcumin. This addition may alter the TK of the curcuminoids, potentially increasing the bioavailability and hepatotoxicity. After a review of the current evidence, it is concluded that the claim with many supplements that piperine improves the bioavailability of curcuminoids is questionable with high uncertainty. The addition of piperine at relatively low concentrations appears to be a potential promotional or marketing tool from the producers with limited scientific evidence supporting these claims.

98. Regarding the curcuminoid concentrations in supplements and the safety implications of long-term intake of these based on the studies presented, it is concluded that if consumption was based on the label guidance this should not pose a significant risk to the vast majority of the population even if there is minor exceedance of the ADI. However, substantial exceedances of the ADI represent a potential health risk to humans.

99. In rare individuals, lower consumption rates may pose the risk of adverse effects particularly if other medicines are being taken concomitantly and in people with certain underlying conditions such as latent impairment of biliary function.

100. The Committee has reviewed all available data regarding the recent reports of hepatotoxicity following consumption of curcumin and have concluded that there is a link to turmeric exposure because the effects occurred upon challenge and were reversed after withdrawal. The symptoms are consistent with an idiosyncratic reaction.

101. Furthermore, some of the other 'novel' supplement types such as micellar, nano, and micro formulations should be assessed in further detail, with regard to their pharmacokinetics and therefore their impact on curcuminoid bioavailability. This further detail is requested regardless that they only potentially make up a likely small percentage of the supplement market at present, as they may become more popular in the future.

Contamination of raw, ground turmeric and curcumin supplements

102. Contamination of raw turmeric with Pb is a result of either growth of turmeric on lead rich soil or intentional adulteration with lead chromate. It has been reported that lead chromate, a Pb-based colour, is sometimes used to enhance the appearance of turmeric. As a result, raw or ground turmeric could potentially contain high levels of Pb.

103. After the Italian incident in 2018 and 2019 (see paragraphs 15 to 17), Italy's National Institute of Health concluded that a contaminant was unlikely to be the underlying cause. Furthermore, the recent 2021 survey of 30 turmeric products and the 2022 survey of 70 turmeric spice powder products did not show any concentrations of Pb in any of the samples above the ML of 3 mg/kg for supplements, and in only one spice powder sample, which had a Pb concentration at 2.25 mg/kg, above a recent ML set by the EU of 1.5 mg/kg. These data add to the evidence base that the hepatotoxic effects noted with taking turmeric is more likely due to the curcuminoids than heavy metal contamination. In addition, the clinical picture is not that typically observed following Pb exposure. Therefore, it is concluded that after the results of the recent product surveys, lead (Pb) contamination of turmeric products are likely not the reason for incidents such as the hepatoxicity reported in the Italian cases. However, it is still uncertain why this incident occurred as a cluster of adverse effects.

104. On evaluation of the other trace element concentrations from the recent study by Fera Science Ltd (Fera Science Ltd, 2022), the metal concentrations across all of the products tested were extremely variable. This

can be attributed to the geographical variation of the source of the products, and / or the other varying additives within supplements. Concentrations of trace elements (metals) that are relatively higher than the average across that product type have been described and evaluated in Annex B to this statement. However, no calculated exposures for any trace elements, if taking the supplements as described on their labels, would exceed any HBGVs, where HBGVs exist.

Summary and conclusions

105. Turmeric is the common name for the rhizome (underground stem) of Curcuma longa L., a perennial herb cultivated in tropical and subtropical regions of the world.

106. Curcumin (E 100) is a dicinnamoylmethane dye obtained from turmeric authorised as a food additive in the EU. It has been evaluated by JECFA, the SCF and EFSA. An ADI of 0 - 3 mg/kg bw had been established based on a reproductive toxicity study by JECFA in 2004 (FAO/WHO, 2004a) and was confirmed in the evaluation by EFSA in 2010.

107. The consumption of turmeric and/or curcumin either raw, powdered or in supplements has become increasingly popular due to the purported health benefits.

108. Curcumin has low bioavailability, however, in supplements, synthetic forms of curcumin or chemical alterations are sometimes used to increase its bioavailability, thus potentially altering its toxicity profile. The claim of many supplements that piperine improves the bioavailability of curcuminoids is questionable with high uncertainty. Ten of the 15 supplements recently surveyed in 2021 contained piperine, 6 of them at > 1% concentration.

109. Consumption of turmeric/curcumin as part of the diet from its use as a food additive or as a spice generally leads to exposures that are below the

dietary ADI. However, when consumed in high quantities for its purported health benefits, or via the intake of supplements, occasional exceedances of the ADI can occur. In a recent curcuminoid survey of 15 supplements when following the dosage advice on the label, 2 of these would lead to exposures above the ADI. It is concluded that if consumption was based on the label guidance there may be minor exceedances of this dietary ADI, but should not pose a significant risk to the population.

110. The Committee have reviewed all available data regarding recent reports of hepatoxicity and have concluded that, despite the limited data available, there is reasonable evidence for a link to turmeric consumption because the effects occurred upon challenge and were reversed after withdrawal. The symptoms are consistent with an idiosyncratic reaction. The occurrence of a contaminant (e.g. heavy metals) as the reason for the recent incidents of hepatoxicity is unlikely.

111. In rare individuals, consumption of turmeric at the levels found in supplements, even at low concentrations (i.e., leading to exposures below the ADI) may pose a risk of adverse effects to the liver, due to an idiosyncratic response. Individuals prone to this response may be genetically susceptible, for example, those carrying the HLA-B*35:01 allele. However, the individual would not know they are susceptible before taking a supplement. This possibility of an unexpected idiosyncratic response should be considered when providing guidance on the use of such supplements.

112. The Committee agree that substantial exceedances of the ADI represent a potential health risk to humans, especially if other medicines are being taken concomitantly and for individuals with altered hepato-biliary function.

113. Other ‘novel’ supplement types such as micellar, nano, and micro formulations should be assessed in further detail, with regard to their pharmacokinetics and therefore their impact on curcuminoid bioavailability.

This is the area of largest concern. This further detail is requested regardless that they only make up a likely small percentage of the supplement market at present, as they may become more popular in the future.

List of Abbreviations and Technical terms

ADI	Acceptable Daily Intake
AFSCA	Belgium's Federal Agency for Food Chain Safety
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AUC	Area Under the Curve
As	Arsenic
BDMC	Bisdemethoxycurcumin
BfR	German Federal Institute for Risk Assessment
BMDL	Benchmark Dose Level
Cd	Cadmium
CO_2	Carbon Dioxide
CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
Cr	Chromium
DILIN	United States Drug-Induced Liver Injury Network
DMC	Desmethoxycurcumin
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
EXPOCHI	Exposure Assessments For Children In Europe
FAO	Food and Agricultural Organisations of the United Nations
GD	Gestation Day
GGT	Gamma-Glutamyl Transferase
HBGVs	Health-Based Guidance Values

Hg	Mercury
HPLC	High Performance Liquid Chromatography
IARC	International Agency for Research on Cancer
IDH	Idiosyncratic Drug Hepatotoxicity
JECFA	Joint FAO-WHO Expert Committee Report on Food Additives
mg	Milligrams
mg/kg bw/day	Milligrams per Kilogram Bodyweight per Day
MPL	Maximum Permitted Levels
ML	Maximum Level
mRNA	Messenger Ribonucleic Acid
NDA Panel	Panel on Nutrition, Novel Foods and Food Allergens
NDS	National Diet and Nutrition Survey
NOAEL	No-Observed-Adverse-Effect Level
Pb	Lead
PK	Pharmacokinetic
SBP	Systolic Blood Pressure
SCF	Scientific Committee for Food
SD	Standard Deviation
TDI	Tolerable Daily Intake
TK	Toxicokinetic
UK	United Kingdom
WHO	World Health Organisation

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Annex B to TOX/2022/68

Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Second draft statement on the potential risk to human health of turmeric and curcumin supplements

Introduction

1. The information presented in this annex should be read in conjunction with the main draft statement on the potential risk to human health of turmeric and curcumin supplements. It contains further detailed information relating to past COT discussions on the safety of curcuminoids and turmeric. This includes discussion on the derivation of a Health Based Guidance Value for curcumin, hepatitis**,** idiosyncratic drug hepatotoxicity and curcuminoids in relation to toxicity covering both animal and human studies. Detailed exposure data for turmeric in food and evaluation of trace element contamination from a recent survey are also included.

Toxicity

Establishment of a Health Based Guidance Value

2. In 1975, the SCF evaluated curcumin (chemical name: diferuloylmethane). They considered that curcumin (from natural foods) could be classified as a colour and although an ADI could not be established it was nevertheless acceptable for use in food (SCF, 1975).

3. In 1995, JECFA evaluated the results of toxicology and carcinogenicity studies in rats and mice administered turmeric oleoresin containing 79-85 % curcuminoids conducted by the National Toxicology Program (NTP, 1993).

After 15 months of treatment, absolute and relative liver weights were increased in both male and female mice in the mid- and highest-dose groups relative to controls. The No Observed Adverse Effect Level (NOAEL) for liver enlargement was 2000 mg/kg in the diet, equal to 220 mg/kg bw/day. On the basis of this NOAEL and a safety factor of 200, JECFA established a temporary ADI of 0-1 mg/ kg bw and extended it, pending the submission of the results of a reproductive toxicity study with curcumin for review in 1998 (FAO/WHO, 1995).

4. In 2004, JECFA noted that the turmeric oleoresin used in the NTP (1993) study did not comply with the current specification for curcumin. JECFA withdrew the temporary ADI and established an ADI for curcumin of 0-3 mg/kg bw based on a NOAEL of 250 mg/kg bw/day for significant decreases in the average bodyweights of Wistar rat F2 generation pups in a reproductive toxicity study dosed at 960 – 1100 mg/kg bw/day and application of a safety factor of 100 (FAO/WHO, 2004).

5. In this study, Wistar rats were fed diets containing curcumin (> 90 % purity) at doses equal to 0, 130-140, 250-290 and 850-960 mg/kg bw/day in males, and 0, 160, 310-320 and 1000-1100 mg/kg bw/day in females. The total period of treatment was 21 weeks for the parental generation and 24 weeks for the F1 generation. No treatment-related clinical signs of toxicity during the study were reported.

6. Significant decreases in the average weights of the F2 generation pups were observed at days 1 and 7 at the intermediate dose, and on days 7, 14 and 21 at the high dose. These decreases represented < 10 % of the average weight of the concurrent controls and were reported to be within the range of the historical control data. There were no other effects on general health, body weight, pup survival or fertility indices in either generation. JECFA considered the effect on pup weight seen at the intermediate dose (equal to 250-320 mg/kg bw/day) to be incidental and therefore a NOEL. (FAO/WHO, 2004).

7. In 2010, based on the study used by JECFA, the EFSA ANS panel concluded that the present database supported an ADI of 3 mg/kg bw/day, also based on significant decreases in the average bodyweights of Wistar rat F2 generation pups (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010).

8. EFSA ANS panel (2010) also reported human studies where volunteers were exposed to relatively high doses of curcumin either via single dose or for up to several months. Based on the results, for dose levels up to 12,000 mg/day, only short-term and semi-chronic adverse effects, such as gastrointestinal effects, headache and rash were observed, but without clear dose-relationship.

Hepatitis

9. Hepatitis is the general term for inflammation of the liver. This has a range of clinical presentations varying in duration, severity and eventual outcome. The initial symptoms of hepatitis are often non-specific but in the later stages of the disease the symptoms reflect impairment of various liver functions. Laboratory evidence of liver cell damage can often be detected in asymptomatic patients but significant impact on the synthetic, metabolic and excretory functions of the liver eventually leads to symptoms such as bruising secondary to lack of clotting factors, encephalopathy caused by failure to convert ammonia to urea, and itching when bile salts are deposited in the skin instead of being eliminated in the bile. The liver has a remarkable ability to regenerate after damage but often fails to replicate the original complex cellular architecture necessary for normal function and instead produces cirrhosis, a combination of fibrous tissue and regenerative nodules.

10. In the UK, the most common causes of liver injury are fatty infiltration of the liver or viral infection, but toxicants (including alcohol), genetic storage disease and autoimmune processes can also lead to liver damage. In a proportion of patients, no ready explanation can be found for liver damage

however severe. Toxicant-induced hepatitis, usually caused by drugs, is not uncommon but usually resolves when the relevant chemical exposure ceases. In some cases, however, cellular damage is severe and the outcome can be fatal. In a few patients severe liver disease may develop, even when the initial response is mild, due to individual susceptibility (idiosyncratic liver disease).

11. Identifying a cause for an episode of hepatitis depends upon a history of exposure to chemicals, drugs or contact with sources of hepatitis infection, together with laboratory investigations. Infection with many of the hepatitic viruses can be identified either by demonstrating an antigenic part of the virus or a specific antibody response to the virus in the blood. Autoimmune disease can be diagnosed from the pattern of antibodies to specific cellular components such as from the mitochondria or nuclei and from the clinical picture of other organ involvement. Damaged liver cells tend to leak enzymes into the blood and some clue as to the site of greatest damage within the liver can be gleaned from the pattern of these enzymes in the blood, with transaminases, particularly alanine aminotransferase (ALT), being released from damaged parenchymal cells and alkaline phosphatase being released from cells lining the bile ducts.

Morphology of hepatitis

12. The morphological appearances of different types of hepatitis are often similar (Ferrell, 2000). Pathological features of acute hepatitis include swelling and ballooning of hepatocytes and cell necrosis affecting single cells, groups of cells adjacent to portal tracts, or extensive confluent areas. Kupffer cells are actively phagocytic and within the portal tracts there are increased numbers of chronic inflammatory cells. There may also be increased numbers of inflammatory cells in the hepatic parenchyma.

13. The defining feature of active chronic hepatitis is infiltration of lymphocytes from portal tracts with associated death of liver cells, so called interface hepatitis. This in time is associated with fibrosis. Sometimes the amount of inflammation is less, and a biopsy fails to show interface hepatitis.

The presence of plasma cells or discrete lymphoid aggregates may suggest the possibility of a viral cause. Some storage disorders, for example Wilson's disease and copper accumulation, and alpha 1 antitrypsin deficiency, show morphological evidence of a chronic active hepatitis. (Ferrell, 2000)

Idiosyncratic drug hepatotoxicity

14. Idiosyncratic drug hepatotoxicity (IDH) occurs in 1/500 to 1/50,000 individuals exposed to a particular drug (the prevalence of idiopathic hepatitis in the community is estimated to be 1/100,000) (Kaplowitz, 2005). IDH has been associated with a variety of pharmaceutical drugs as well as food supplements, notably kava kava. IDH is variable, person specific and occurs for a number of drugs, but also does not occur for many others. Idiosyncratic events are not just caused by the drug itself but by reactions unique to the individual who is exposed to it (Apica and Lee, 2014). However, without the drug there would be no effect. IDH is generally too rare to be detected in clinical trials, though elevated ALT levels may be an indicator. As a general rule, an ALT level greater than three times the upper level of normal is considered to be a sensitive indicator of liver toxicity (the marker is not completely specific since muscle injury may elevate ALT levels). While this is nearly universally described for idiosyncratic liver toxicants, it is not always predictive of overt idiosyncratic toxicity as many patients with elevated ALT levels do not develop IDH.

15. Two types of IDH can occur. Allergic IDH occurs with a short latency period and involves the adaptive immune system. Symptoms may include fever, rash or eosinophilia. It is not well understood why some individuals have or subsequently develop allergic IDH. However, it is likely due to an individual's genetics, body chemistry at a particular time of life, frequent or multiple drug exposures and/or the presence of an underlying disease. Non-allergic IDH has none of the above features. There can be a long latency period, where there may have been months of normal liver function test results prior to the occurrence of IDH. Symptoms vary depending on the drug

but can include, for example, gastrointestinal irritation and vomiting (American Academy of Allergy Asthma & Immunology, 2020).

Curcuminoids and hepatotoxicity: Animal studies

Short-term studies of toxicity

Mice

16. Dietary turmeric powder (0 %, 0.2 %, 1.0 %, 5.0 %, equivalent to 0, 400, 2000, 10000 mg/kg bw/day) or ethanolic turmeric extract (ETE, 0%, 0.05 %, 0.25 %, equivalent to 0, 100, 500 mg/kg bw/day) for 14 days, at doses reported to be cancer preventive in model systems, were found to be hepatotoxic in mice. The diferuloylmethane contents of the turmeric powder and ETE were not reported. Exposure of mice to dietary turmeric or ETE did not have any significant effect on body weight/ liver weight or liver to body weight ratios. Animals exposed to 0.2 % turmeric showed coagulative necrosis in liver. Livers from mice receiving 1.0 % and 5.0 % turmeric showed extreme degenerative changes with necrosis. Coagulative necrotic foci surrounded by a zone of regeneration were also evident. Similar changes were also seen in animals treated with 0.05 % and 0.25 % ETE. Necrotic changes in liver, the principal effect, was seen in 6/6 animals from 5.0 % turmeric, 3/6 from 1.0 % turmeric and 3/6 animals from 0.2 % turmeric. Similarly, 3/6 animals from 0.05 % as well as 0.25 % ETE also showed these alterations. Liver from mice receiving control diet showed normal ultrastructure. In the liver of the animals receiving 5.0 % or 1.0 % turmeric diet or 0.25 % or 0.05 % ETE, some of the parenchymal cells had round nuclei consisting of clumped or densely marginated chromatin. The cytoplasm consisted of numerous pleomorphic vacuolated mitochondria filled with dense bodies, surrounded by rough or smooth endoplasmic reticulum and free ribosomes, and an increased number of glycogen particles and Golgi complexes with vesicles (Kandarkar et al., 1998).

17. Sub-chronic oral toxicity of turmeric and ETE was studied in female Swiss mice and Wistar rats fed turmeric powder (0, 1 and 5 %) and ethanolic turmeric extract (0, 0.05 and 0.25 %) through the diet for 14 and/or 90 days. The curcuminoid content of the ETE was approximately 98%. The administration of a high dose of turmeric (5 %) for longer duration (90 days) resulted in a significant reduction in body weight gain, alterations in absolute and / or relative liver weights, and hepatotoxicity i.e., focal necrosis or focal necrosis with regeneration both in mice and rats. In mice, lower doses of turmeric (i.e., 0.2 or 1 % for 14 days) also showed hepatotoxicity and they were found to be more susceptible to turmeric-induced hepatotoxicity than rats (Deshpande et al., 1998).

18. In a 13-week study, groups of 10 male and 10 female B6C3F1 mice were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin, which were estimated to deliver average daily doses of 0, 150, 750, 1700, 3850, or 7700 mg/kg bw to males and 0, 200, 1000, 1800, 4700 or 9300 mg/kg bw to females (NTP 1993). The major component of the oleoresin was identified as curcumin (79 to 85 %). The percent composition was monitored periodically at the study laboratory with free-acid titration and high-performance liquid chromatography methods, and no change in composition was observed. There were no deaths attributed to turmeric oleoresin and the final mean body weight gains and final mean body weights of all exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that by the controls. Absolute and relative liver weights of male mice that received 5000 ppm and male and female mice that received 10000, 25000 and 50000 ppm were significantly greater than those of the controls. These changes were not considered adverse. Clinical findings in mice included stained fur, and discoloured faeces and urine. According to NTP, there were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters, and there were no chemical related histopathologic lesions. EFSA ANS panel (2010) concluded that the no-effect level with respect to gross and microscopic pathological changes was 7700 and 9280

mg/kg bw/day in males and females, respectively, which were the highest doses tested.

Rats

19. Liju et al. (2013) investigated the acute and sub-chronic toxicity of turmeric essential oil (TEO) from Curcuma longa L. Acute administration of TEO was as a single oral dose of up to 5 g/kg bw, and a 13-week sub-chronic toxicity study was performed at doses of 0, 0.1, 0.25 and 0.5 g/kg bw/day in Wistar rats. There were no substance-related mortalities, adverse clinical signs or changes in body weight, water and food consumption during the acute and sub-chronic studies. Indicators of hepatic function such as aspartate aminotransferase (AST), ALT and alkaline phosphatase (ALP) were unchanged in treated animals compared to untreated animals. Oral administration of TEO for 13 weeks did not alter total cholesterol, triglycerides, markers of renal function, serum electrolyte parameters and histopathology of tissues.

20. In a 28-day study, curcumin (purity > 98 %) was administered to Sprague Dawley rats through the diet at dose levels of 0, 26.1, 84.8, 224,8, 459.7 and 1117.8 mg/kg bw/day. Clinical chemistry did not reveal major signs of liver damage associated with administration of diferuloylmethane. cDNA microarray experiments were performed on hepatic RNA. Diferuloylmethane altered the expression of 12 genes. Three of these were related to peroxisomes (phytanoyl-CoA dioxygenase, enoyl-CoA hydratase; CYP4A3). Increased cyanide insensitive palmitoyl-CoA oxidation was observed. The authors concluded that these data suggest that diferuloylmethane is a weak peroxisome proliferator in rats (Stierum et al., 2008).

21. In a 13-week study, groups of 10 male and 10 female F344/N rats were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane), estimated to deliver average daily doses of 0, 50, 250, 480, 1300, or 2600 mg/kg bw to males and 0, 60, 300, 550, 1450, or 2800 mg/kg bw to females. All rats survived until the end of the

study. The final mean body weight of males receiving 50000 ppm was 5 % lower than that of the controls. Feed consumption by exposed male and female rats was similar to that of controls. The absolute and relative liver weights of female rats and the relative liver weights of male rats receiving ≥ 5000 ppm were significantly greater than those of the controls. According to the NTP, these increases may have been due to mild hepatocellular swelling or hypertrophy. In the clinical chemistry, urinalysis, and hematologic assessment, no differences were observed that were considered by the NTP to be biologically significant. Clinical findings included stained fur, and discoloured faeces and urine of exposed animals. Mild to moderate hyperplasia of the mucosal epithelium was observed in the cecum and colon of male and female rats that received 50000 ppm. A NOAEL was not concluded by the study authors. (NTP 1993).

22. A six-month toxicity study of curcuminoids extracted from the powdered dried rhizome of Curcuma longa was performed in six groups of 15 Wistar rats of each sex. The extract was reported to contain 58-67 % curcuminoids. The water control group received 5 ml of water/kg bw/day, while the tragacanth (plant-derived gum) control group received 5 ml of 0.5 % tragacanth suspension/ kg bw/day orally. Three treatment groups were given the suspension of curcuminoids powder at doses of 10, 50 and 250 mg/kg bw/day. The fourth treatment group, or the recovery group, also received 250 mg/kg bw/day of curcuminoids for six months, but two weeks of no curcuminoids treatment elapsed before the time of termination. The growth rate of male rats receiving curcuminoids at 50 mg/kg bw/day was significantly higher than that of the tragacanth control group. Curcuminoids did not produce any significant dose-related changes of haematological parameters. In male animals receiving 250 mg/kg bw/day of curcuminoids, actual and relative liver weights and the level of alkaline phosphatase (ALP) were significantly higher than those of the two controls, but the ALP level was still within a normal range. There appeared to be a higher incidence of mild degree of liver fatty degeneration and adrenocortical fatty degeneration in this group of animals, however the incidence was not significantly different from

that of the two controls. The authors concluded that at higher doses, curcumin may affect the function and morphology of the liver in a reversible manner. The EFSA ANS Panel (2010) concluded that due to the lack of knowledge on the diferuloylmethane content and nature of the extract tested, the study could not be used to assess the safety of diferuloylmethane (Chavalittumrong et al., 2002).

Chronic toxicity

Two years study in mice

23. Groups of 60 male and 60 female B6C3F1 mice were fed diets containing 0, 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane) for 103 weeks, which were estimated to deliver average daily doses of 0, 220, 520, or 6000 mg/kg bw to males and 0, 320, 1620, or 8400 mg/kg bw to females (NTP 1993). Nine or ten mice from each exposure group were evaluated after 15 months. Survival of exposed male and female mice was similar to that of the controls. The mean body weight of female mice receiving 50000 ppm was slightly lower (up to 12 %) than that of the controls from about week 25. The final mean body weights of males that received 50000 ppm and females that received 10000 and 50000 ppm were significantly lower than those of controls. The final mean body weights of other exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that of the controls throughout the study. The absolute and relative liver weights of male and female mice receiving 10000 and 50000 ppm were significantly greater than those of the controls at the 15-month interim evaluation. There were no clinical findings related to toxicity. No biologically significant differences were observed in hematologic parameters. The alkaline phosphatase values of male and female mice that received 10000 and 50000 ppm were significantly higher than those of controls at the 15-month interim evaluation. The incidences of hepatocellular adenoma in male and female mice receiving 10000 ppm (the mid dose group), but not those in mice

receiving 2000 or 50000 ppm, were significantly increased (male: 25/50, 28/50, 35/50, 30/50; female: 7/50, 8/50, 19/51, 14/50). The number of male and female mice in the 10000 and 50000 ppm groups with multiple hepatocellular neoplasms compared with controls was statistically significantly increased. However, JECFA concluded that this effect was not dose-related and that curcumin is not a carcinogen (FAO/WHO 1995). In addition, the EFSA ANS Panel (2010) noted that all statistically significant effects noted by the NTP refer to benign neoplastic lesions (adenomas). The EFSA Panel noted that the effects observed were not dose-dependent, were in line with historical control values and were not consistent across sexes and/or species. The Panel noted moreover that “hepatocellular tumours occurring in untreated and treated B6C3F1 mice are not relevant for humans”. Therefore, the Panel agreed with JECFA that curcumin was not carcinogenic.

Two years study in rats

24. Groups of 60 male and 60 female F344/N rats were fed diets containing 0, 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane) for 104 (males) or 103 (females) weeks, which were estimated to deliver average daily doses of 0, 80, 460, or 2000 mg/kg bw to males and 0, 90, 440, or 2400 mg/kg bw to females. Nine or 10 rats from each exposure group were evaluated after 15 months. Survival of exposed male and female rats was similar to that of the controls. The final mean body weights of all exposed male rats and female rats receiving 2000 and 10000 ppm were similar to those of the controls. The final mean body weights of male and female rats that received 50000 ppm were slightly lower (up to 10 %) than those of the controls throughout much of the study. Feed consumption by exposed male and female rats was similar to that of controls throughout the study. The absolute and relative liver weights of female rats receiving 10000 or 50000 ppm were significantly greater than those of controls at the 15-month interim evaluation. There were no clinical findings related to toxicity. In male and female rats receiving 50000 ppm the haematocrit values, haemoglobin concentrations and erythrocyte counts at

the 15-month interim evaluation were significantly lower than those in the controls. In addition, platelet counts in male and female rats that received 50000 ppm and reticulocyte counts in male rats that received 50000 ppm were significantly higher than those in the controls. No biologically significant differences were observed in clinical chemistry parameters, however, a NOAEL was not concluded by the study authors (NTP 1993).

Curcuminoids and hepatotoxicity: Case studies in humans

25. In addition to the reported cases in Italy, several cases of liver toxicity associated with intake of curcumin supplements have been reported in the literature.

26. In Australia, from Luber et al., (2019) a 52 year old woman presented to her general practitioner with a one-week history of nausea, pruritus, and painless jaundice with associated pale stools and dark urine. This occurred approximately one month following commencement of one tablet per day of a 'High Potency' turmeric supplement (375 mg curcuminoids and 4 mg black pepper per tablet), along with a flaxseed oil supplement and occasional diclofenac use for arthritic pain. (N.B. this supplement leads to an intake of 204.6 % of the ADI of 3 mg/kg bw/day). She had no prior history of liver disease and had normal liver function tests (LFTs) three months before. Her medical history was notable only for oligoarticular osteoarthritis.

27. Upon admission, all oral medications and supplements were ceased. She was found to have a bilirubin concentration of 162 μmol/L with a hepatocellular injury profile on liver function tests (ALT 2591 U/L, AST 1770 U/L, ALP 263 U/L, and GGT 370 U/L). With progressive jaundice over the subsequent days she was referred to the emergency department, at which point her bilirubin peaked at 536 μmol/L.

28. Due to lack of significant improvement by day four of admission, a liver biopsy was performed. Histology showed nonspecific inflammatory changes

with generally preserved hepatic architecture and no fibrosis. She was discharged on day 12 of admission (bilirubin 260 μmol/L, ALT 1232 U/L) with the presumptive diagnosis of diclofenac induced liver injury. By two months after admission her liver function tests had normalised (bilirubin 21 μmol/L, ALT 33 U/L) and she was discharged from the clinic. At this point she recommenced the turmeric supplement as sole therapy for her arthritis. Three weeks later her nausea recurred and repeat liver function tests showed an acute hepatitis (ALT 2093 U/L, AST 1030 U/L, and bilirubin 60 μmol/L). She was advised to cease the turmeric supplement, and two months later her liver function tests had again normalised.

29. The turmeric supplements were sent for analysis by a validated liquid chromatography mass spectrometry method. Results were compared to a toxicology library containing approximately 1400 compounds, including medications, illicit drugs, and over-the-counter medicines. A further sample was analysed by inductively coupled plasma mass spectrometry for the presence of trace elements. The turmeric supplement tested negative for drugs, adulterants and toxic heavy metals. (Luber et al. 2019).

30. A 55 year old man was found to have an asymptomatic transaminitis at a routine check-up. His background history included idiopathic thrombocytopenic purpura, hypertension, gout, and osteoarthritis, with regular medications including long-term telmisartan, atenolol, and lercanidipine. He had no known liver history with normal liver function tests one year prior. His only new medication was commencement of a turmeric supplement five months prior to testing. He was referred to a hepatologist and underwent a screen for causes of acute hepatitis. Abdominal ultrasonography showed diffuse steatosis. A drug reaction was suspected, and the turmeric supplement was ceased. Follow-ups occurred over the subsequent four months. Near normalisation of liver function tests occurred by one month (ALT 96 U/L, bilirubin 10 μmol/L) with further improvement by four months after cessation (ALT 46 U/L, bilirubin 11 μmol/L). The turmeric supplement was the presumed cause of the hepatitis. The turmeric supplement was not identified,

thus further analysis on it could not be performed and thus dose information is unknown. (Luber et al. 2019).

31. In the US, reported by Suhail et al., (2020) a 61 year old female with polycystic liver disease presented with fatigue, dark urine and polyarthralgias for one week. She denied alcohol use. Physical examination demonstrated right upper quadrant abdominal tenderness. Laboratory findings were notable for elevations of aspartate aminotransferase 1553 mg/dL, alanine aminotransferase 2607 mg/dL, alkaline phosphatase 246 mg/dL and total bilirubin 1.6 mg/dL with a direct component of 1 mg/dL. Hepatic synthetic function was intact. Medications included naproxen and ergocalciferol (vitamin D) with no changes four years prior to the onset of transaminitis. Viral infections were ruled out. Autoimmune work-up yielded positive antinuclear antibody (1:250) with normal anti-smooth muscle antibody and serum IgG levels. Abdominal Doppler was negative for portal or hepatic vein thrombosis. Magnetic resonance cholangiopancreatography did not show any biliary duct pathology. It was discovered that the patient had been taking turmeric supplements for 6 months. A liver biopsy demonstrated pan lobular hepatitis with early parenchymal collapse suggestive of a morphologic counterpart of acute hepatitis and hepatocellular pattern of injury. The patient was thought to have drug-induced liver injury from turmeric pills that were discontinued and she was discharged with prednisone. Her LFTs normalized after 3 weeks, after which, her prednisone was tapered off.

32. Suhail et al. (2019) noted that the temporal association of liver injury in the patient, normalisation of LFTs upon withdrawal and improvement with steroids implicate the turmeric supplement as the likely causative agent of liver injury. The Roussel-Uclaf Causality Assessment Method (RUCAM) scale, which attempts to codify causality of drug toxicity into objective criteria, was eight in the patient indicating a probable adverse drug reaction. A negative serological workup and normalisation of LFTs following the discontinuation of steroids further solidify this conclusion.

33. In another case in the US reported by Lukefahr et al., (2018) a 71 year old woman was found to have an asymptomatic transaminitis at routine check-up. Her medical history included hypothyroidism, Raynaud's syndrome, osteoarthritis, hypertension, dyslipidaemia, irritable bowel syndrome, and diverticulosis, with regular medications including amlodipine, metoprolol, and atenolol. A 'low cost' turmeric supplement (of unknown product identification) was taken according to label recommendations for a period of 8 months prior to transaminitis testing. The patient was referred to a gastroenterologist. Laboratory and biopsy findings led to a diagnosis of autoimmune hepatitis. Treatment was limited to withdrawing use of turmeric supplements. AST and ALT decreased significantly within 30 days of discontinuation and normalised by 13 months. In this case, the patient (not the clinicians) hypothesised that the turmeric may have been the cause of the elevated liver transaminases and elected to cease its use.

34. Subsequent reassessment of the liver biopsy by Lukefahr et al., (2018) revealed auto-fluorescent inclusions in the pigment-laden histiocytes, with an excitation/emission spectrum consistent with curcumin, or possibly lipofuscin. Histiocyte fluorescence, which was not noted in liver biopsy specimens from patients with unrelated disorders, was quenchable by treatment with Sudan Black B (SBB), as has been reported for lipofuscin. However, because the authors also documented complete SBB quenching of curcumin autofluorescence in fixed cultured cells specifically loaded with curcuminoids, the authors could not ascertain with certainty whether the histiocyte inclusions were composed of lipofuscin, a lysosomal degradation product and/or curcuminoids derived from the turmeric supplement that the patient was still consuming at the time of the biopsy.

35. In September 2018, before the cluster of Italian cases in 2019, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) considered several clinical studies with turmeric preparations involving patients with digestive disorders. Although a possible effect in improving symptoms was seen, firm conclusions could not be drawn due to

limitations in the study design, for example only one study compared turmeric with a control group. However, the HMPC considered the effectiveness of these preparations for relief of mild digestive problems to be plausible and there is evidence that they have been used safely in this way for at least 30 years (including at least 15 years within the European Union). Thus, the HMPC concluded that turmeric preparations (which cover turmeric ground powders and extracts) can be used (only by adults) for relief of mild problems with digestion, such as feelings of fullness, slow digestion and flatulence. The EMA considered that side effects of dry mouth, flatulence and stomach irritation may occur. If symptoms continue for longer than two weeks or worsen while taking the medicine, a qualified healthcare practitioner should be consulted (EMA (European Medicines Agency), 2018).

Exposure from curcuminoids in food

36. The relative proportions and total concentration of curcuminoids within turmeric rhizomes vary depending on the variety grown and the conditions of cultivation (Li et al., 2011) (Table 1).

Table 1. Percentage composition of curcuminoids in turmeric powders and oleoresin extracts (adapted from Li et al., 2011).

Curcuminoid	**Composition in turmeric powders (mean) (% dry weight)**	**Composition in turmeric oleoresin extracts (mean ± s.d.) (% dry weight)**
Diferuloylmethane	2.86	19.5 ± 2.07
Demethoxycurcumin	1.47	8.31 ± 1.13
Bisdemethoxycurcumin	1.36	6.22 ± 0.88
Total	5.69	34.0 ± 4.08

37. The EFSA ANS panel (2010) estimated dietary exposure to diferuloylmethane in children and adults using national consumption data with maximum permitted levels (MPLs) specified in Directive 94/36/EC (EC 1994)

(tier 2 approach), and maximum reported use levels (tier 3 approach). Estimates of dietary exposure to diferuloylmethane obtained from these approaches are presented in Table 2.

38. For adults (> 18 years old), the EFSA ANS Panel (2010) estimated the exposure based on the UK consumption survey as the UK population is considered to be one of the highest consumers of soft drinks in Europe and individual food consumption data (UK National Diet and Nutrition Survey (NDNS), 2000-2001) are available (Tennant D., 2007, 2006). For children (1-10 years old), the Panel estimated exposure based on the Dietary Exposure Assessments for Children in Europe (EXPOCHI) project. The EXPOCHI project details individual food consumption data from eleven European countries (Belgium, France, the Netherlands, Spain, Italy, Finland, Sweden, Czech Republic, Cyprus, Greece and Germany). As the UK is not included in the EXPOCHI consortium, estimates for UK children (1.5 - 4.5 years old) were made by the Panel with the use of individual food consumption data (UK NDNS, 1992-1993) (Tennant D., 2007, 2006).

Table 2: Estimates of dietary exposure to curcumin in the UK adult population and in children from the EXPOCHI study and UK NDNS data.

Maximum permitted level (tier 2):	**UK adult exposure (> 18 years old) to curcumin (mg/kg bw/day)**	**Children (UK & EXPOCHI , 1-10 years old) exposure to curcumin (mg/kg bw/day)**
Mean exposure	0.9	0.5-3.8
Exposure 97.5th %ile	3.3	1.2-7.2
Maximum reported use levels (tier 3):	**UK adult exposure (> 18 years old) to curcumin (mg/kg bw/day)**	**Children (UK & EXPOCHI , 1-10 years old) exposure to curcumin (mg/kg bw/day)**
Mean exposure	0.8 (1.0 *)	0.5-3.4 (0.7-3.6 *)
Exposure 97.5th %ile	2.0 (2.6 *)	1.1-7.1 (1.6-7.6 *)

* Includes dietary exposure to diferuloylmethane from turmeric powder added to food as a spice and curry powder (see Table 3).

39. In tier 2, the main contributor to curcumin exposure from the UK adult diet was non-alcoholic flavoured drinks (46 %). The main contributors to the estimates of mean curcumin exposure for UK children (and children considered by the EXPOCHI consortium) were non-alcoholic beverages (13-55 %), fine bakery wares (e.g., biscuits, cakes, wafer) (12-43 %), desserts, including flavoured milk products (12-45 %), and sauces, seasonings, pickles, relishes, chutney and piccalilli (11-42 %).

40. In tier 3, the main contributor to curcumin exposure from the UK adult diet was non-alcoholic flavoured drinks (50 %). The main contributors to the estimates of mean curcumin exposure for UK children (and children considered by the EXPOCHI consortium) were fine bakery wares (e.g., biscuits, cakes, wafer) (13-47 %), desserts (including flavoured milk products) (13-52 %), non-alcoholic beverages (15-57 %) and sauces and seasonings (11-45 %).

41. The exposure assessment in tier 3 does not take into account the use of turmeric as a spice in cooking. The addition of turmeric spice in cooking was estimated to contribute to the dietary exposure of diferuloylmethane by the EFSA ANS panel (2010) (Table 3).

Table 3. Estimates of dietary exposure to diferuloylmethane from ingestion of spice added to food and curry powder in adults in children.

Exposure from spice added to food *	**Adult (18-64 years old) curcumin exposure (mg/kg bw/day)**	**Children (5-12 years old) curcumin exposure (mg/kg bw/day)**
Mean	0.1 (n = 66)	0.1 (n = 7)
97.5th %ile	0.3 (n = 66)	0.2 (n = 7)

Exposure from curry powder added to food *	**Adult (18-64 years old) curcumin exposure (mg/kg bw/day)**	**Children (5-12 years old) curcumin exposure (mg/kg bw/day)**
Mean	0.1 (n = 91)	0.1 (n = 21)
97.5th %ile	0.3 (n = 91)	0.3 (n = 21)

* The use of turmeric as a spice added to foods and used in home-made recipes was assessed using data from Irish adults (1379 adults, aged 18-64 years) and children (594 children, aged 5-12 years) (Harrington et al., 2001; IUNA (Irish Universities Nutrition Alliance), 2005). The dietary intake of curry powder was also considered, as turmeric powder is a widespread ingredient of it (approximately 30 % depending on the blend).

42. The above information is indicative of the current exposures to curcumin and/or turmeric as part of the diet (food colour and as a spice). However, consumption of raw and powdered turmeric in large quantities to promote wellbeing is becoming increasingly popular. Based on information readily available on the internet it is proposed that to benefit from turmeric's antioxidant effects, one should consume between 500 to 1000 mg of curcuminoids per day. It is suggested that one teaspoon of fresh or powdered turmeric contains 200 mg of curcumin. Consumptions at the proposed levels, could lead to exposures to curcumin above the recommended ADI.

Contamination of raw, ground turmeric and curcumin supplements

Heavy metals

43. From the recent survey undertaken by Fera Science Ltd (Fera Science Ltd, 2022) all samples were analysed for 69 trace elements which included the heavy metals Pb, Hg, As, and Cd.

44. Twenty-nine of the 30 samples tested had heavy metal concentrations of low concern, i.e., below the maximum level (ML) set for supplements by EC

1881/2006 or below the EU ML set for root spices by the amendment EU 2021/1317 (due to the recent date, this amendment to the EU regulation is not in UK legislation). For supplements, the MLs are 3 mg/kg for Pb, 1 mg/kg for Cd and 0.1 mg/kg for Hg. For root spice powders the EU ML is 1.5 mg/kg for Pb. Arsenic does not have a ML set for supplements, but all concentrations, bar two samples) were below the 0.2 mg/kg ML set for white rice by EU 2015/1006.

45. One sample, a turmeric spice powder, contained a Pb concentration approximately 10 times higher than the majority of other samples analysed, at 2.25 mg/kg. This would be over the amended recent EU ML of 1.5 mg/kg for root spice powders. This sample also had the second highest concentration of chromium (Cr) at 2.11 mg/kg, which may indicate adulteration with lead chromate. If this sample were taken as a supplement at, for example, a teaspoon per day (4g) the total exposure of lead from this source alone would be 0.13 µg/kg bw/day for a 70 kg adult. This is approximately 25% of the estimated dietary exposure of 0.5 µg/kg bw day, equivalent to the $BMDL_{01}$ of 12 µg/L blood Pb concentration, for effects of Pb on developmental neurotoxicity (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010).

46. When the heavy metal results for supplement samples were compared against spice powders and fresh turmeric there were no clear trends or significant differences between the groups (supplements against powder & fresh samples).

47. On evaluation of the other trace element from the 30 samples, results that differed by greater than the mean plus 2 x the standard deviation and 5 x the mean of that sample type (i.e. fresh, powder or supplement) are summarised in Table 4. Table 5 summarises the exposure of each of the trace elements if taking the supplement as advised on the label, alongside comparison of a Health Based Guidance Value (HBGV) if applicable. No

estimated exposures for any trace elements would exceed any HBGVs where HBGVs exist.

Table 4. List of other trace elements (i.e. not including Pb, Hg, As or Cd) from turmeric product samples, where the concentration is greater than 5 x the mean concentration and the mean concentrations plus 2 x standard deviations for that product type.

Sample code	Sample type	Element	Concentration (mg/kg)	Mean concentration of product type (mg/kg)	Increased fold change from mean
TU03	Supplement	Titanium	281	29	9.7
TU03	Supplement	Niobium	0.16	0.023	7.0
TU06	Supplement	Molybdenum	1.9	0.21	9.0
TU06	Supplement	Uranium	0.57	0.079	6.6
TU06	Supplement	Tin	0.16	0.025	6.4
TU07	Supplement	Thallium	0.10	0.012	8.3
TU07	Supplement	Caesium	0.09	0.014	6.4
TU07	Supplement	Zinc	38	7.3	5.2
TU07	Supplement	Barium	50	9.8	5.1
TU10	Powder	Tungsten	0.039	0.0072	5.4
TU12	Supplement	Copper	114	8.6	13.3
TU15	Supplement	Yttrium	4.1	0.56	7.3
TU15	Supplement	Antimony	0.24	0.033	7.3
TU15	Supplement	Palladium	0.11	0.019	5.8
TU15	Supplement	Lanthanum	1.3	0.23	5.7
TU15	Supplement	Calcium	323,000	63,913	5.1
TU17	Supplement	Beryllium	0.124	0.016	7.8
TU17	Supplement	Antimony	0.19	0.033	5.8

Table 5. Summary of exposure of each of the trace elements from Table 4 for an adult taking the supplement as advised on the label, alongside comparison of a Health Based Guidance Value (HBGV) if applicable

Element	Concentration (mg/kg)	Advised consumption of supplement (g/day)	Exposure from product* (µg/kg bw/day)	HBGV or other reference value (µg/kg bw day)	HBGV reference
Titanium	281	0.42	1.69	n/a	n/a
Niobium	0.16	0.42	0.0010	n/a	n/a
Molybdenum	1.9	0.35	0.010	26 (TUI)	(Institute of Medicine (US) Panel on Micronutrients, 2001)
Uranium	0.57	0.35	0.0029	0.6 (TDI)	(WHO, 2012)
Tin	0.16	0.35	0.00080	2 (p-TDI)	(FAO/WHO, 2004)
Thallium	0.10	0.92	0.0013	0.01 (p-RFD)	(EPA, 2009)
Caesium	0.09	0.92	0.0012	n/a	n/a
Zinc	38	0.92	0.50	1000 (TDI)	(FAO/WHO, 1982)
Barium	50	0.92	0.66	200 (TDI)	(SCHER, 2012)
Tungsten #	0.039	7	0.0022	n/a	n/a
Copper	114	1	1.6	70 (ADI)	(EFSA, 2022)
Yttrium	4.1	4.7	0.28	145.5 (TDI)	(Kowalczyk et al., 2022)
Antimony	0.24	4.7	0.016	6	(WHO, 2003)
Palladium	0.11	4.7	0.0074	n/a	n/a

Lanthanum	1.3	4.7	0.087	51.3 (TDI)	(Kowalczyk et al., 2022)
Calcium	323,000	4.7	21,733	35,714 (TUI) **	(SCF, 2003)
Beryllium	0.124	0.3	0.00053	2	(WHO, 2009)
Antimony	0.19	0.3	0.00081	6	(WHO, 2003)

* Assumes a 70Kg adult consumes the supplement as stated on the label.

** Assumes a 70Kg adult to derive the TUI.

Tungsten concentration from a spice powder not a supplement. A conservative estimate of 4g per day if consumed as a supplement has been used for the exposure calculations.

TUI = Tolerable Upper Intake.

TDI = Tolerable Daily Intake.

p-RFD = Provisional Reference Dose.

ADI = Acceptable Daily Intake.

List of Abbreviations and Technical Terms

ADI	Acceptable Daily Intake
AFSCA	Belgium's Federal Agency for Food Chain Safety
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
As	Arsenic
BDMC	Bisdemethoxycurcumin
BMDL	Benchmark Dose Level
Cd	Cadmium
CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
Cr	Chromium
DMC	Desmethoxycurcumin
EFSA	European Food Safety Authority
ETE	Ethanolic Turmeric Extract
EU	European Union
EXPOCHI	Exposure Assessments For Children In Europe
FAO	Food and Agricultural Organisations of the United Nations
GGT	Gamma-Glutamyl Transferase
HBGVs	Health-Based Guidance Values
Hg	Mercury
HMPC	Committee on Herbal Medicinal Products
IDH	Idiosyncratic Drug Hepatotoxicity
JECFA	Joint FAO-WHO Expert Committee Report on Food Additives
LFTs	Liver Function Tests
mg	Milligrams
mg/kg bw/day	Milligrams per Kilogram Bodyweight per Day
MPL	Maximum Permitted Levels
ML	Maximum Level

NDA Panel	Panel on Nutrition, Novel Foods and Food Allergens
NDNS	National Diet and Nutrition Survey
NOAEL	No-Observed-Adverse-Effect Level
NTP	United States National Toxicology Program
p-RFD	Provisional Reference Dose
Pb	Lead
ppm	Parts Per Million
SCF	Scientific Committee for Food
SD	Standard Deviation
SSB	Sudan Black B
TEO	Turmeric Essential Oil
TDI	Tolerable Daily Intake
TUI	Tolerable Upper Intake
UK	United Kingdom
U/L	Units per Litre
WHO	World Health Organisation

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