Meeting

Discussion paper on the potential risk to human health of Turmeric and curcumin supplements - following a recent product survey

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Background

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 Toxicity (COT) has been asked to comment on the risk to human health from turmeric and curcumin in their various forms.

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. The most recent draft statement discussed by the Committee is provided in Annex A.

4. Minutes from the three most recent Committee meetings regarding turmeric have been provided in Annex A. 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. Unfortunately, the undertaking of this FSA-funded survey was delayed due to laboratory prioritisation implications caused by the COVID 19 pandemic.

5. This discussion paper presents the findings from this turmeric supplement survey. The survey of 30 products was undertaken by Fera Science Ltd. 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). The full Fera Science Ltd final report is given in Annex B.

6. Since the previous papers were discussed by the Committee, a recent EFSA opinion on the safety of tetrahydrocurcuminoids from turmeric as a novel food was published (EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) et al., 2021). Tetrahydrocurcuminoids are transformation products of curcuminoids with potentially greater bioavailability, stability and solubility in aqueous solutions.

Introduction

7. 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. 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 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).

8. Many of the purported pharmacological properties of turmeric have been attributed to 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".

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

10. 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.

11. 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 3 mg/kg bw/d had been established by JECFA in 2004 based on a reproductive toxicity study and this was re-confirmed in the evaluation by EFSA in 2010 (WHO/FAO, 2004; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010).

12. It is estimated that supplement intake leads to exposures that are several magnitudes higher than the ADI. Furthermore, synthetic forms of turmeric and curcumin, or conjugation with other chemicals such as piperine, are used to increase absorption, thus altering its toxicokinetic profile. Therefore, the COT 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 toxicokinetic profiles and increased bioavailability. Thus, the levels determined as of low safety concern in food may not be relevant for supplements.

13. A known safety issue with curcumin and/or turmeric is contamination. Contamination with lead is a result of either turmeric grown on lead rich soil or intentional adulteration with lead chromate. Often lead chromate, a lead-based colour, is used to enhance the appearance of turmeric. As a result, raw or ground turmeric could potentially contain high levels of lead.

14. Turmeric powder can be adulterated with powders of other species of Curcuma which may be toxic. For example, the powder of Curcuma zedoaria, a common adulterant in turmeric powder, is known to be toxic; 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). Furthermore, in supplements, there has been a number of reported cases that involved adulteration with nimesulide, a nonsteroidal anti-inflammatory drug known to cause liver problems.

15. Based on IndustryARC's business intelligence report, the global curcumin market size was around $56-58 million in 2018 and is forecast towards progression at a global Compound Annual Growth Rate of 9% to 10% during the forecast period (2019-2025) (IndustryARC, 2019). Europe is the second biggest market with a total market share of 29.15% by revenue and was projected to be the fastest growing market in terns of value, with an estimated compound annual growth rate of 9.5% between 2018-2025. Regarding market shares, pharmaceutical applications are dominating the curcumin market by revenue and are projected to achieve a market size of $62.43 million by 2025. Food applications are the second major market share and they were projected to grow by 40% by 2025.

Supplements and reported hepatotoxicity

16. 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) (Will Chu, 2019a).

17. Whilst the AFSCA said 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 adopted a warning for the labelling of the supplements in question (to take effect from 31st December 2019), advising against their use for 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.

Toxicokinetics

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

19. Approximately 75% of the administered dose was excreted 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). 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).

20. Numerous studies in animals have evaluated the level of curcumin after administration and found that either no curcumin or its metabolites, or only low levels, were detected in serum or tissue (Ravindranath and Chandrasekhara, 1981; Shen and Ji, 2012). Further details are provided within the previous draft statement (Annex A).

21. In humans, the same dose of curcumin did not allow the calculation of these half-life values because the serum curcumin levels were below the detection limit at most of the time points in most of the experimental subjects. However, this may not be the case with exposure from supplements.

22. In supplements it is common practice to alter the curcumin product to change its metabolism and enhance its bioavailability. This can be achieved with methods such as the use of liposomal curcumin, curcumin nanoparticles, the use of curcumin phospholipid complex and the use of structural analogues of curcumin that are water soluble. The use of adjuvants that interfere with glucuronidation is also popular. For example, piperine, the major active ingredient in black pepper, has been shown to increase the absorption of curcumin by up to 2000% (Hewlings and Kalman, 2017). Therefore, the toxicokinetics of curcuminoids taken as a supplement may be very different to the kinetics when consumed via conventional dietary exposure as a flavouring. In the meeting of the COT on 10th March 2020 members concluded that synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered toxicokinetic profiles and increased bioavailability (see minutes provided in Annex A).

Toxicity

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

23. In 1975, the Scientific Committee for Food (SCF) evaluated curcumin. No ADI was set by SCF as they considered that curcumin (from natural foods) could be classified as colour for which an ADI could not be established but which is nevertheless acceptable for use in food (SCF, 1975).

24. 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, issued 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).

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

26. 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 for a few 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.

27. 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 toxicokinetic profiles and increased bioavailability. Thus, the levels determined as of low safety concern in food may not be relevant for supplements.

28. In a very recent review of tetrahydrocurcuminoids (transformation products of curcuminoids by hydrogenation), EFSA proposed a safe exposure concentration for adults, excluding pregnant and lactating women, of 2 mg/kg bw / day, equivalent to 140 mg/day for a 70Kg adult. This was derived from a NOAEL of 200 mg/kg bw / day in a rat reproduction and development study with an uncertainty factor of 100 (inter and intra species variability) applied. Hepatoxic effects were not observed in a 90 day repeated dose oral toxicity study up to the highest dose evaluated of 400 mg/kg bw/day. (EFSA Panel on Nutrition, Novel Foods and Food

Allergens (NDA) et al., 2021)

Hepatitis (further details provided in Annex A)

29. 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.

30. 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 common and often resolves when the relevant chemical exposure ceases. In some cases, however, cellular damage is severe and the outcome can be fatal.

31. 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 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 mitochondria 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 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.

32. Idiosyncratic drug hepatotoxicity (IDH) occurs in1/500 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 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.

33. Two types of IDH occur. Allergic IDH occurs with a short latent period and involves the adaptive immune system. Symptoms may include fever, rash or eosinophilia. Non-allergic IDH has none of the above features. There is a long latency period, where there may have been months of normal liver function test results prior to the occurrence of IDH.

Turmeric and hepatotoxicity

34. Full details of the relevant animal studies were provided in the COT discussion paper TOX/2019/52 and summarised in the draft statements discussed by the committee (Annex A).

35. 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.

36. 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 (Lukefahr et al., 2018; Luber et al., 2019; Suhail et al., 2020).

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

37. Raw turmeric could be contaminated with lead as a result of either turmeric grown on lead rich soil or intentional adulteration with lead chromate (Cowell et al., 2017). Often lead chromate, a lead-based colour, is used to enhance the appearance of turmeric. As a result, raw or ground turmeric could potentially contain high levels of lead.

38. Lead 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 lead in blood. Lead in bone is

released into blood during pregnancy and becomes a source of exposure to the developing fetus (WHO, 2017).

39. The 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. The respective BMDLs derived from blood lead levels in µg/L (corresponding dietary intake values in µg/kg bw/d) were: developmental neurotoxicity BMDL01, 12 (0.50); effects on systolic blood pressure (SBP) BMDL01, 36 (1.50); effects on prevalence of chronic kidney disease BMDL10, 15 (0.63). The Panel highlighted that by protecting children, who are far more sensitive, from the developmental effects of lead, 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 (of 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.

Exposure assessment

Exposure from use in food

40. 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, demethoxycurcumin, and bisdemethoxycurcumin) (EC, 2008). Directive 94/36/EC 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).

41. The previous discussion paper (TOX/2019/52) and subsequent draft statement (Annex A) discussed dietary exposure using turmeric consumption data from the EFSA ANS 2010 evaluation which used data from the UK National Diet and Nutrition Survey (NDNS) 2000 - 2001 and the European (EXPOCHI) project.

42. Dietary exposure was below the JECFA 2004 ADI of 3 mg/kg bw/day (FAO/WHO, 2004) for both adults and children when using UK NDS data and taking the mean exposure using both maximum reported occurrence concentrations and maximum permitted levels.

Exposure through turmeric supplements

43. In addition to exposure to curcumin through a normal diet, turmeric supplements can also be taken. These can be as bought ‘over the counter’ supplements or by ‘self-dosing’, through consumption of spices in large quantities.

44. 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, 1992). 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, dichloromethane, and 1,2-dichloroethane, and 50 mg/kg for ethanol, methanol, and isopropanol (FAO/WHO, 1992). The extraction methodology used affects the curcuminoid content (37-55 %) (Li Shiyou, et al., 2011), and the essential oil content (< 25%) (Braga et al., 2003) of the turmeric oleoresin (Table 1).

Table 1. Preparation and composition of turmeric products that are commercially available as dietary supplements (adapted from Li et al. 2011).

Commercial product name	Preparation	Composition
Turmeric powder	Prepared from dried rhizomes of C. longa	0.58-3.14 % curcumin (dry weight), and other curcuminoids
Turmeric oleoresin extract	Treat turmeric powder with organic solvents	37-55 % curcuminoids, < 25 % essential oil
Turmeric oil extract	Treat turmeric powder with steam distillation or supercritical CO2 extraction	Essential oil from leaves usually dominated by monoterpenes whilst oil from rhizomes mainly contains sesquiterpenes

Curcumin powder	Purify turmeric oleoresin through crystallisation	> 90 % curcuminoids, and minor amounts of essential oil

45. Whilst curcuminoids are responsible for the yellow-orange colour of turmeric, it is the volatile sesquiterpenes present in the rhizome's essential oil that are responsible for its aroma and taste (Li et al. 2011). The major sesquiterpenes in turmeric oil extract are α-, β-, and Ar-turmerone (Li et al. 2011), which can together account for > 40 % of the essential oil present in turmeric rhizomes (Stanojević et al., 2015). Turmerone possesses diverse pharmacological activities that include antioxidant and antimutagenic activities (Jayaprakasha et al., 2002). Turmeric oil extract can be prepared in various ways, for example through the treatment of turmeric powder with steam distillation, supercritical CO2 extraction (Li et al. 2011), or by evaporating the organic solvent of a crude turmeric oleoresin extract (Funk et al., 2010).

46. 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 be 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).

Assessment after new sample survey - Curcuminoids

47. Previously in discussion paper TOX/2019/52 and the subsequent draft statement (Annex A) a range of supplement information was taken to estimate exposure to curcuminoids. Since these papers were written a sample survey has been commissioned by the FSA and undertaken by Fera Science Ltd. The full report can be found in Annex B.

48. 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. These consisted of supplements (n=15), ground/powdered turmeric (n=10) and fresh turmeric root (n=5). One of the fresh samples arrived dried.

49. All samples were analysed in duplicate for the curcuminoids: curcumin, BDMC and DMC as well as the black pepper derived alkaloid piperine. Tables 2 and 3 summarise the results for total curcumin and total curcuminoids for each sample type, i.e. supplement, dried powder or fresh.

Table 2. Summary of curcumin concentrations of sample's surveyed, expressed as % concentration in whole product.

Sample type	n	Mean	SD	Max	Min
Supplement	15	8.71	11.6	45.3	0.958
Powder	10	1.37	0.374	2.01	0.720
Fresh *	4	0.299	0.102	0.46	0.199

*Turmeric root sample which did not arrive fresh removed from summary of results.

Table 3. Summary of total curcuminoids (sum of curcumin, BDMC and DMC) concentrations of sample's surveyed, expressed as % concentration in whole product.

Sample type	n	Mean	SD	Max	Min
Supplement	15	10.40	12.4	49.2	1.683
Powder	10	2.44	0.736	3.92	1.233
Fresh *	4	0.592	0.175	0.84	0.409

*Turmeric root sample which did not arrive fresh removed from summary of results.

50. It has been reported that piperine increases the bioavailability of curcuminoids (Hewlings and Kalman, 2017), potentially significantly altering the

toxicokinetics, however the extent to which this occurs at differing piperine and curcuminoid concentrations is unknown. Piperine is often added to supplements and the concentrations measured by Fera in the survey and detailed in the report are given in Table 4, alongside the total curcuminoid concentrations for reference. Also, within Table 4 the expected daily exposure of both sets of compounds is provided based upon the dose advice on the label of the sample.

Table 4. Piperine and total curcuminoids concentrations in supplements analysed as an absolute % concentration and at concentrations of exposure using the labelled recommended dose.

Sample code	Mean piperine concentration (absolute, %)	Mean piperine daily exposure (mg / kg bw / day)*	Mean total curcuminoids concentration (absolute, %)	Mean total curcuminoids daily exposure (mg / kg bw / day)*
TU02	0.12	0.020	1.68	0.29
TU03	< 0.01	n/a	1.70	0.10
TU05	0.36	0.065	13.9	2.47
TU06	9.08	0.454	2.87	0.14
TU07	< 0.01	n/a	4.34	0.57
TU08	< 0.01	n/a	11.4	1.72
TU12	1.82	0.260	49.2	7.02
TU13	< 0.01	n/a	4.82	2.73
TU15	0.76	0.508	9.06	6.10

TU17	18.2	0.779	28.9	1.24
TU18	0.06	0.010	2.04	0.36
TU20	3.50	0.125	5.88	0.21
TU21	3.38	0.492	3.54	0.52
TU25	< 0.01	n/a	12.3	1.26
TU30	13.9	0.498	4.55	0.16

* Calculated using an adult body weight of 70 kg (EFSA Scientific Committee, 2012) and maximum recommended daily dosage on the product label.

51. Of the supplements sampled, 5 had total curcuminoids over 10%, with one at almost 30% (sample TU17) and one at almost 50% (TU12) absolute concentration. Of the 5 supplements providing concentrations of total curcuminoids on the label all results were within ± 20 % of the stated concentration.

52. From this survey, taking the recommended doses daily according to the supplement's label, exposure concentrations for a 70 kg adult would range from 0.1 to 7 mg/kg bw/day. Taking supplement TU12 would contribute a further approximate 3-fold increase in exposure to curcuminoids than would be expected from dietary exposure, highlighted and discussed in the previous draft statement (Annex A).

53. Ten of the 15 supplements contained detectable concentrations of piperine with 6 of those > 1 %, which could potentially alter the toxicokinetics of the curcumin compounds consumed within the same supplement. One of the samples (TU05) containing piperine did not state this on the label. Three of the supplements contained piperine at approximately 10% or higher, with TU15 and TU17 for example having high concentrations of both curcuminoids and piperine. Taking the TU15 and TU17 supplements at the recommended doses results in an exposure estimate of 6.1 and 1.2 mg/Kg bw/day respectively for a 70 Kg adult.

54. 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 2.5 teaspoons a day as recommended by a source on the internet (Laurence, 2021) exposures were generally below the ADI of 3 mg/kg bw/day with one exception (sample TU10). These results are presented in Table 5.

Table 5. Total curcuminoids concentrations in spice powder samples analysed, as an absolute % concentration and evaluating exposure using a 2.5 teaspoon a day consumption estimation and an ADI of 3 mg/kg bw/day.

Sample code	Mean total curcuminoids concentration (absolute, %)	Mean total curcuminoids daily exposure (mg / Kg bw / day)*	% ADI
TU01	2.47	2.47	82.5
TU04	1.24	1.24	41.3
TU09	2.40	2.40	79.9
TU10	3.92	3.92	130.6
TU11	2.60	2.60	86.8
TU14	2.78	2.78	92.8
TU16	2.38	2.38	79.2
TU22	1.23	1.23	41.1
TU23	2.87	2.87	95.6
TU24	2.46	2.46	82.0

* Calculated using an adult body weight of 70 kg (EFSA Scientific Committee, 2012) and a dosage of 2.5 teaspoons (taken as 7g).

Assessment after new sample survey - Heavy Metals

55. From the recent survey undertaken by Fera Science Ltd, described above, all samples were analysed for 69 trace elements which included the heavy metals Pb, Hg, As, and Cd. The full Fera final report is given in Annex B.

56. All samples tested had heavy metal concentrations of low concern, i.e. below the maximum recommended levels set for supplements by EC 1881/2006. For supplements these are 3 mg/kg for Pb, 1 mg/kg for Cd and 0.1 mg/kg for Hg. As does not have a MRL set for supplements, but all concentrations, bar two samples (TU05 and TU15) were below the 0.2 mg/kg MRL set for white rice by EU 2015/1006. Table 6 presents these results for each sample tested for the 4 heavy metals. The full Fera report in Annex B provides results for all 69 trace elements.

Table 6. Pb, As, Hg and Cd concentrations (mg/kg) of the 30 samples analysed.

Sample code	Sample type	Lead (Pb)	Arsenic (As)	Mercury (Hg)	Cadmium (Cd)
TU01	powder	0.071	0.035	<0.005	0.013
TU02	supplement	0.033	0.017	<0.005	0.009
TU03	supplement	0.094	0.102	<0.005	0.219
TU04	powder	0.116	0.036	<0.005	0.037
TU05	supplement	0.26	0.448	<0.005	0.055
TU06	supplement	0.097	0.084	<0.005	0.037
TU07	supplement	0.288	0.095	<0.005	0.221

TU08	supplement	0.092	0.031	<0.005	0.017
TU09	powder	0.203	0.053	<0.005	0.015
TU10	powder	2.25	0.133	<0.005	0.086
TU11	powder	0.638	0.039	<0.005	0.032
TU12	supplement	0.023	0.01	<0.005	<0.005
TU13	supplement	<0.005	<0.005	<0.005	<0.005
TU14	powder	0.231	0.034	<0.005	0.015
TU15	supplement	0.111	0.286	<0.005	0.107
TU16	powder	0.159	0.068	<0.005	0.02
TU17	supplement	0.03	0.015	<0.005	<0.005
TU18	supplement	0.152	0.052	<0.005	0.065
TU19	fresh	0.072	0.047	<0.005	0.014
TU20	supplement	0.012	<0.005	<0.005	<0.005
TU21	supplement	<0.005	<0.005	<0.005	<0.005
TU22	powder	0.066	0.093	<0.005	0.013
TU23	powder	0.05	0.02	<0.005	0.011

TU24	powder	0.151	0.052	<0.005	0.019
TU25	supplement	0.024	<0.005	<0.005	<0.005
TU26	fresh	0.011	<0.005	<0.005	<0.005
TU27	fresh	0.018	<0.005	<0.005	<0.005
TU28	fresh	0.018	0.007	<0.005	0.01
TU29	fresh	0.018	<0.005	<0.005	<0.005
TU30	supplement	0.008	<0.005	<0.005	<0.005

57. Sample TU10, 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 sample also had the second highest concentration of Chromium (Cr) at 2.11 mg/kg which may indicate potential adulteration with lead chromate. If sample TU10 was taken as a supplement at, for example, 2.5 teaspoons a day (approximately 7g) the total exposure of lead from this consumption alone would be 0.23 µg/kg bw/day for a 70Kg adult. This is approximately 2 fold lower than the BMDL10 of 0.5 µg/kg bw day for the effects on developmental neurotoxicity (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010).

58. When comparing heavy metal results for supplement samples against spice powders and fresh turmeric there were no clear trends or significant differences between the groups when evaluating the results using a students t-test (supplements against powder & fresh samples).

Risk Characterisation

Curcuminoids

59. As discussed in the previous discussion paper and draft statement (Annex A) for raw and powdered turmeric / curcumin, consumption as part of the normal diet (from its use as an additive and spice) would lead to exposures that are

generally within the ADI of 3 mg/kg bw/day.

60. There is high uncertainty regarding the risk for 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 curcumin in humans is well tolerated up to doses of 114 mg/kg bw/day, though minor symptoms of nausea or diarrhoea may occur. Long-term studies are lacking, however.

61. With regard to dietary turmeric supplements, the recent survey shows that a small proportion of the available products would lead to high exposure of curcuminoids i.e. exposures at or above the ADI of 3 mg/kg bw/day. However, crucially COT concluded from previous discussions that this ADI is not relevant for supplements. This is because as shown in this survey, 10 of the 15 supplements analysed contained piperine which alters the toxicokinetics of the curcuminoids, likely increasing the bioavailability (paragraph 22) and potential hepatotoxicity. This could potentially alter the toxicity profile of the chemicals. Furthermore, information on the long-term toxicity of curcumin and its altered forms used in supplements is lacking and safety margins of health-based guidance values are potentially eroded with consumption of supplements. This potentially increases the risk of adverse effects, particularly in vulnerable individuals if taking these supplements regularly.

62. As presented in the previous draft statement (Annex A), based on the available information from both animal and human studies, the COT concluded that “it appears that there is a potential link between hepatoxicity and curcuminoids because the effects occurred upon challenge were reversed after withdrawal. The symptoms are considered to be an idiosyncratic drug reaction. However, a role for a possible contaminant cannot be ruled out. The animal data is consistent with the human data.”

Contamination of raw, ground turmeric and curcumin supplements

63. Contamination of raw turmeric with lead is a result of either turmeric grown on lead rich soil or intentional adulteration with lead chromate. Often lead chromate, a lead-based colour, is used to enhance the appearance of turmeric. As a result, raw or ground turmeric could potentially contain high levels of lead.

64. From the survey of 30 turmeric products no sample contained Pb concentrations above the MRL of 3 mg/kg for supplements. These data add to the small evidence base that the hepatotoxic effects noted with taking turmeric is

more likely due to the curcuminoids rather than heavy metal contamination.

Summary and conclusions

65. 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.

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

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

68. Curcumin has low bioavailability, however, in supplements, synthetic forms of curcumin or chemical alterations are used to increase its bioavailability by up to 2000%, thus potentially altering its toxicity profile. Ten of the 15 supplements recently surveyed contained piperine, 6 of which at > 1% concentration.

69. 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 ADI. However, when consumed in high quantities for its purported health benefits, or via the intake of supplements, substantial exceedances of the ADI can occur. From this recent curcuminoid survey of 15 supplements and when following the dosage advice on the label, 2 of these would lead to concentrations above the ADI set for dietary exposure. There is lack of information on the chronic toxicity of turmeric/curcumin thus the risk to health cannot be determined. Furthermore, comparison with the dietary ADI is potentially not relevant due to the likely toxicokinetic alterations of the curcuminoids in supplements when combined with other chemicals such as piperine.

70. Regarding the recent reports of hepatotoxicity, the Committee has previously reviewed all available data and have concluded that there is a link to turmeric because the effects occurred upon challenge and were reversed after withdrawal. The symptoms are consistent with an idiosyncratic drug reaction. However, a role for a possible contaminant cannot be ruled out.

71. There are known heavy metal contamination issues in turmeric and curcumin supplements, however from this recent UK survey of 30 turmeric products no heavy metal concentrations above regulatory levels were found.

72. The Committee previously agreed 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.

Questions for the Committee

73. The Committee are asked to consider:

1. Would the Committee want to consider tetrahydrocurcuminoids exposure now or in the future?

2. What are the Committee's conclusions regarding the use of piperine and / or any other potential adjuvants as potential synergistic additives within supplements?

3. In light of these new survey results does the committee have any further discussion points or conclusions regarding the safety of turmeric supplements available in the UK?

4. Does the Committee have any other comments on this paper?

Secretariat

March 2022

List of Abbreviations and Technical terms

ADI	Acceptable Daily Intake
AFSCA	Belgium's Federal Agency for Food Chain Safety
ALT	Alanine Aminotransferase

ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
As	Arsenic
BDMC	Bisdemethoxycurcumin
BMDL	Benchmark Dose Level
Cd	Cadmium
CO2	Carbon Dioxide
CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
Cr	Chromium
DMC	Desmethoxycurcumin
EC	European Commission
EFSA	European Food Safety Authority
EXPOCHI	Exposure Assessments For Children In Europe
FAO	Food and Agricultural Organisations of the United Nations
Hg	Mercury

HPLC	High Performance Liquid Chromatography
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
MRL	Maximum Recommended Level
NDA Panel	Panel on Nutrition, Novel Foods and Food Allergens
NDS	National Dietary Survey
NOAEL	No-Observed-Adverse-Effect Level
Pb	Lead
SBP	Systolic Blood Pressure
SCF	Scientific Committee for Food
SD	Standard Deviation
UK	United Kingdom
WHO	World Health Organisation

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