Meeting

# Discussion paper on the potential risk to human health of turmeric and curcumin supplements

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 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 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 (Annex A), 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). Minutes from this meeting are provided in Annex A.

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 and imported food surveillance programs.

7. From the COT discussion on the 29th March 2022 it was noted that there were potentially new papers in the literature evaluating the bioavailability of curcuminoids, and in particular the potential toxicokinetic (TK) changes that may, or may not, occur with adjuvant compounds such as piperine.

8. This discussion paper presents an updated review of turmeric supplement safety. Taking into account the recently commissioned product surveys, a review of recent literature on bioavailability impact / pharmacokinetics (PK) with adjuvant compounds on curcuminoids and an updated review of curcuminoid safety when these supplements are taken long term. Also, an updated market ‘snapshot’ has been discussed, in regard to supplements that have unusual or novel contents such as synthetic curcuminoids or curcuminoids within micro or nanoparticles for marketing claims of ‘greater absorption’.

# Introduction

9. 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).

10. 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 DMC and BDMC are also present within turmeric rhizomes. These compounds are collectively called “curcuminoids”.

11. 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 curcumin supplements.

12.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.

13. 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 (FAO/WHO, 2004a; EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010).

14. It is the usage 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.

15. It is estimated that supplement intake potentially 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 potentially increase absorption, thus altering the TK profile. The addition of piperine into turmeric supplements is a very common practice. Therefore, the COT in 2020 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.

16. A known safety issue with curcumin and/or turmeric is contamination. Contamination with heavy metals for example is a result of either turmeric grown on contaminated soil or intentional adulteration with, for example, lead chromate. Often lead chromate, a Pb-based colour, is used to enhance the appearance of turmeric. Other yellow chromate compounds 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.

17. 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.

18. 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 terms 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.

19. Curcuminoid supplements are generally sold as a capsule containing 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 uncertain 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.

20. Stohs et al., (2020) review of modified forms of curcumin supplement products 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).’

**Supplements and reported hepatotoxicity**

21. Between December 2018 and 20$^{th}$ 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, 2019).

22. 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 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 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

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

24. 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). Curcuminoids are sensitive to phase II metabolism in the gastrointestinal tract, with glucuronides identified as being the dominant metabolite (Wang et al., 2019).

25. Furthermore, it is also reported that the low bioavailability of curcuminoids is due to low membrane permeability. With the underlying mechanism relating to an active reflux by P-glycoprotein and a n-octanol/water partition coefficient (log P) of approximately 4 (Ji et al., 2016; Jamwal, 2018). Therefore, the low bioavailability of curcuminoids can be attributed to a fast metabolism, rapid excretion and low membrane permeability.

26. 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).

27. 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.

28. In supplements it is common practice to alter the curcumin product to change its metabolism and enhance its bioavailability, by addressing the metabolism, membrane permeability or both. This can be achieved with methods such as the use of liposomal curcumin, curcumin nanoparticles (as part of a nano or microemulsion (Liu, Smart and Pannala, 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.

29. The use of adjuvants is currently the most widely adopted modification of turmeric supplements. For example, piperine is the most widely used adjuvant, 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 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 due to the alteration of membrane dynamics (Khajuria, Thusu and Zutshi, 2002) and therefore compounds with lower membrane permeability such as curcuminoids can subsequently be more greatly 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, Thusu and Zutshi, 2002).

30. 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

31. Piperine has been shown to increase the absorption of curcumin in vivo by up to 154% in rats and up to 2,000% in a human study (Shoba et al., 1998). Within this study, piperine was administered at 20 mg/kg concomitantly with curcumin at 2g/kg to Wistar rats (single dose), and at 20 mg/kg in humans with curcumin at 2g total (also a single dose).

32. There is a lack of any further studies providing direct evidence of piperine enhancing the bioavailability of curcumin, however there are several examples of piperine being used to aid the bioavailability of other compounds.

33. Emodin was administered at 20 mg/kg to Sprague-Dawley rats in the absence and presence of 20 mg/kg of piperine, both as a single dose. The area under the curve (AUC) and Cmax of emodin were greatly increased in the rats also dosed with piperine, this was attributed to the inhibition of glucuronidation of emodin (Di et al., 2015).

34. Similarly, in a study using CF-1 mice Lambert et al., (2004) showed an increase in the plasma Cmax and AUC of Epigallocatechin-3-gallate (EGCG) by 1.3-fold when combined with piperine at 70 micromol/kg to 164 micromol/kg EGCG. Again this was attributed to the inhibition of glucuronidation of EGCG (Lambert et al., 2004).

35. In a human study by Bano et al., (1991) piperine was administered at 20 mg daily for 7 days to a cohort of 6 individuals, after a single dose of either propranolol at 40 mg or theophylline at 150 mg. The study found that an earlier Tmax and a higher Cmax and AUC were observed in the subjects who received propranolol with piperine compared to the propranolol only control groups. Likewise, a higher Cmax, longer elimination half-life and a higher AUC were

observed in the subjects who received theophylline with piperine compared to the theophylline only control groups.

36. Based on the in vitro and in vivo studies above, the TK of curcuminoids, taken as a supplement alongside piperine, may be very different to the kinetics when consumed via conventional dietary exposure as a flavouring.

37. However, 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: standard turmeric extract, liquid micellar preparation, piperine-curcuminoid combination, phytosome formulation and a dried colloidal suspension. Curcuminoid doses varied between delivery mechanisms but ranged between 300 and 1,500 mg. 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. Results showed that the AUC, after dose normalisation correction, of both the micellar and dried colloidal products were significantly higher (P (Fança-Berthon et al., 2021).

38. Fanca-Berthon et al., (2021) give several potential reasons for the differences in these findings from the Shoba et al., (1998) human study in the effect of piperine bioavailability when provided concomitantly with curcuminoids:

- The Shoba study had only 8 study participants compared to 30 in the Fanca-Berthon et al. study
- Shoba studied a shorter kinetic duration, sampling after 3 hours compared to 24 hours in the Fanca-Berthon study, which found a Tmax of 6 hours for the parent curcuminoid compounds.
- Shoba only measured the single compound curcumin, compared to the metabolites and other related curcuminoids analysed by 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.'

39. 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). For example, the conclusion of no increase in bioavailability effect by piperine from the Fanca-Berthon et al. (2021) study may have only entered the literature as the authors hypothesis on the increased bioavailability effects on a dried colloidal suspension were vindicated, and the piperine study was undertaken alongside this.

40. Stohs et al., (2020) report that micellar nano / micro formulations of curcuminoid supplements provide a greater increase in bioavailability by as much as 500-fold compared to a non-encapsulated standard curcumin formulation. This was from a 12 person human study, monitoring both free curcuminoids and metabolite concentrations in plasma up to 24 hours after a single dose (Stohs et al., 2018). The micellar encapsulation provides an increase in water solubility and potential protection from metabolism in the gastrointestinal tract.

41. Synthetic forms of curcuminoids were primarily developed for pharmacotherapy purposes. Increases in bioavailability are demonstrated by modifying the compounds to make them more water soluble, for example as a hydrazinonicotinic acid conjugate (Lagisetty et al., 2012).

42. In the meeting of the COT on 10$^{th}$ March 2020 members concluded that synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered TK profiles and increased bioavailability.

# Toxicity

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

43. In 1975, the Scientific Committee for Food (SCF) evaluated curcumin. No ADI was set by the 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).

44. 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).

45. 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, 2004a).

46. 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.

47. 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 (further details provided in Annex A)**

48. 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.

49. 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.

50. 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.

51. 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 many drugs, but also does not occur for many others. Idiosyncratic events are not caused by the drug itself but by reactions unique to the individual who is exposed to them (Apica and Lee, 2014). 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.

52. Two types of IDH 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 (American Academy of Allergy Asthma & Immunology, 2020). Also, having an allergy to one drug predisposes an individual to have an allergy to another unrelated drug. 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.

**Curcuminoids and hepatotoxicity**

53. 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).

54. 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.

55. 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).

56. 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. Conversely, they report curcuminoids have potential hepatoprotective properties. For example, they quote Rahmani et al., (2016) who show a reduced liver fat content and liver transaminases of humans with non-alcoholic fatty liver disease taking 70 mg of curcumin daily for 8 weeks. However, it should be noted that 3 of the authors of the Pancholi et al., (2021) publication are employed by a supplements company.

**Medium to long term safety of curcuminoids**

57. 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.

58. 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).

59. In a double-blind, placebo-controlled study by Petracca et al., (2021) 80 multiple sclerosis patients were enrolled onto a trial, 40 of which 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.

60. 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.

61. Nakagawa et al., (2022) describe a double-blind, placebo-controlled study in 43 patients with knee joint diseases with a treatment and control group. The treatment group were given 180 mg of curcumin daily for 52 weeks. Adverse effects were no worse in the treatment group compared to the control.

62. There are numerous other similar clinical trials in the literature showing the potential long-term safety of curcuminoid consumption at similar or higher concentrations provided in supplements. For example trials reported by Appelboom, Maes and Albert, 2014; Sterzi et al., 2016 and Haroyan et al., 2018.

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

63. Raw turmeric can be contaminated with Pb as a result of either turmeric grown on Pb rich soil or intentional adulteration with lead chromate (Cowell et al., 2017). It has been reported 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 as high as 1,150 mg/kg from an extensive turmeric survey in Bangladesh.

64. 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 to the developing fetus (WHO, 2021).

65. 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 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 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 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 (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

66. 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).

67. A 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.

68. Dietary exposure was below the JECFA 2004 ADI of 3 mg/kg bw/day (FAO/WHO, 2004a) 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**

69. 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.

70. 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, 2003). The extraction methodology used affects the curcuminoid content (37-55 %) (Li, et al., 2011), and the essential oil content (

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, |
| 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 |

71. 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).

72. 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).

73. In supplements it is common practice to alter the curcumin product to change its metabolism and enhance its bioavailability, by addressing the metabolism, membrane permeability or both. 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.

**Assessment after 2021 sample survey - Curcuminoids**

74. 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 in Summer

2021. The final report for this survey can be found in Annex B.

75. 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.

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

77. 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.

78. From the 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 (mean of 1.7 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 increase in exposure to curcuminoids than would be expected from a high dietary exposure (2.6 mg/kg bw/day), highlighted and discussed in the previous draft statement (Table 2 in Annex A).

79. 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.

80. 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 (giving 3.9 mg/kg bw/day for a 70 kg adult).

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

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

82. 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.

83. 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 potential adulteration with lead chromate. If this sample 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 70 kg adult. This is approximately 2 fold lower than the estimated dietary lead exposure of 0.5 µg/kg bw day for the effects of Pb on developmental neurotoxicity, derived from the BMDL01 of 12 µg/L blood Pb concentration (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010).

84. 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).

85. On evaluation of the other trace element results 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 2. The potential toxicity of these metals at these concentrations has not been investigated and the list is given for information only. Overall, the trace element profile of each sample was variable, this is explained by

1. the different geographical sources of the products and therefore the differing background trace element concentrations from the environment the products were derived
2. The varying chemical nature of the different supplement formulations

Table 2. 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 deviation 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 |

86. 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

# Risk Characterisation

### Curcuminoids

87. As discussed in previous discussion papers 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.

88. 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 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 described in this paper (paragraphs 57 to 62) suggest that daily consumption of curcuminoids at concentrations at or above those found in supplements result in no adverse effects.

89. 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 3 mg/kg

bw/day. However, crucially COT concluded from previous discussions that this ADI is not relevant for supplements. This is because as also shown in the 2021 survey, 10 of the 15 supplements analysed contained piperine which may alter the TK of the curcuminoids, potentially increasing the bioavailability (paragraph 31) and hepatotoxicity. This could potentially alter the toxicity profile of the chemicals. However, there is counter evidence from Fança-Berthon et al., 2021 that suggests piperine does not increase bioavailability of curcuminoids.

90. Information on the long-term toxicity of curcumin directly consumed as supplements by healthy individuals 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.

91. 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**

92. Contamination of raw turmeric with Pb is a result of either turmeric grown 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.

93. After the Italian incident in 2018 and 2019 (see paragraphs 21 and 22), Italy’s National Institute of Health did not believe a contaminant was 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 Pb concentrations above the ML of 3 mg/kg for supplements, and only one spice powder sample with Pb concentrations at 2.25 mg/kg was 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 rather than heavy metal contamination.

94. On evaluation of the other trace element concentrations of the recent study by Fera Science Ltd in 2021, the metal concentrations across all of the products tested was 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 metals that are relatively higher than the average across that product type have been described but their impact on consumer safety has not been evaluated in this paper.

## Summary and conclusions

95. 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.

96. 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 (FAO/WHO, 2004a) and was re-confirmed in the evaluation by EFSA in 2010.

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

98. Curcumin has low bioavailability, however, in supplements, synthetic forms of curcumin or chemical alterations are used to increase its bioavailability, thus potentially altering its toxicity profile. However, based on the findings of a recent study, the use of the adjuvant compound piperine may not increase the bioavailability of curcuminoids as previously reported. Ten of the 15 supplements recently surveyed in 2021 contained piperine, 6 of which at > 1% concentration.

99. 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, substantial exceedances of the ADI can occur. From a 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. A comparison with the dietary ADI is possibly not relevant due to the potential TK alterations of the curcuminoids in supplements when combined with other chemicals such as piperine.

100. 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.

101. There are known heavy metal contamination issues in turmeric and curcumin supplements, however from the 2021 and 2022 UK surveys, from a total of 100 turmeric products only one spice powder product with Pb concentrations at 2.25 mg/kg was above a recent ML set by the EU of 1.5 mg/kg.

102. The Committee previously (September, 2019) 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

103. The Committee are asked to consider:

1. Based on the updated literature review and current evidence, do members still conclude that adjuvated curcumin with piperine, which may be used in supplements, could have altered TK profiles and increased bioavailability?
2. Given we believe other novel administration mechanisms in supplements make up only approximately 10% of the market do the committee want to consider these in any greater detail from a TK perspective?
3. Given the conclusions of Italy’s National Institute of Health on their incident in 2018/2019 and the low concentrations of heavy metals found in recent turmeric product surveys do members have further thoughts on the causes of hepatoxicity reported associated with turmeric supplementation consumption?
4. Do members have any concerns regarding any of the other relatively higher concentrations of metals given in Table 2?
5. Does the Committee still conclude that supplements providing higher concentrations of curcuminoids than would be expected from dietary exposure represent a potential health risk to humans?
6. Does the Committee have any other comments on this discussion paper?

## Secretariat

**July 2022**

# 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 |
| AUC | Area Under the Curve |
| 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 |
| GGT | Gamma-Glutamyl Transferase |
| 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 |
| ML | Maximum Level |

| | |
|---|---|
| NDA Panel | Panel on Nutrition, Novel Foods and Food Allergens |
| NDS | National Dietary Survey |
| NOAEL | No-Observed-Adverse-Effect Level |
| Pb | Lead |
| PK | Pharmacokinetic |
| SBP | Systolic Blood Pressure |
| SCF | Scientific Committee for Food |
| SD | Standard Deviation |
| TK | Toxicokinetic |
| UK | United Kingdom |
| WHO | World Health Organisation |

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