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

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

Introduction

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

2. Turmeric is the common name for the rhizome (underground stem) of *Curcuma longa* L (Linnaeus), a perennial herb cultivated in tropical and subtropical regions of the world. India is the largest producer of turmeric, supplying over 90 % of the world's demand (Olojede *et al*., 2009). There are approximately 70 varieties of *C. longa* cultivated in India (Sasikumar, 2005). For centuries, turmeric has been widely used as a powder prepared from the rhizome for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases (Ammon and Wahl, 1991). This powdered form is also known as turmeric.

3. Many of the purported pharmacological properties of turmeric have been attributed to curcuminoids, particularly curcumin (chemical name:

diferuloylmethane). These properties include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities (Alok *et al*., 2015). Curcumin is a polyphenol compound naturally present within turmeric rhizomes. Its derivatives desmethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) are also present within turmeric rhizomes. These compounds are collectively called “curcuminoids”.

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

5. Some turmeric oleoresin extracts and curcuminoid preparations may fall within the scope of the Novel Foods Regulations. Novel food status is assessed on a case-by-case basis and depends on the characteristics of the ingredient and evidence of its history of consumption (HoC) prior to 15 May 1997 in the UK or the EU. Novel foods require pre-market authorisation before being placed on the market in Great Britain. Where uncertainty exists, food business operators may seek a determination from the FSA through the Article 4 consultation process.

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

7. The regulatory framework applicable to curcuminoids depends on their intended use. Curcuminoids used to perform a colouring function in food may

be regulated under food additives legislation, whereas some curcuminoid-containing ingredients may fall within the scope of the Novel Foods Regulations. It is the responsibility of a Food Business Operator (FBO) to verify whether their product would be captured by novel foods regulation before they place the product on the market.

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

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

10. Turmeric powder can be intentionally or unintentionally adulterated with chemical dyes or powders of other species of *Curcuma,* which may be more toxic. For example, the powder of *Curcuma zedoaria,* a common adulterant in turmeric powder, is potentially toxic; the high-protein flour of *C. zedoaria* caused 100 % mortality within 6 days when given daily at 320 g/kg diet to 5 week-old rats. The cause of death was unclear (Latif *et al*., 1979).

Furthermore, in supplements, there have been a number of reported cases that involved adulteration with nimesulide, a nonsteroidal anti-inflammatory drug (NSAID) known to cause liver problems.

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

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

13. In Stohs *et al*., (2020) review of modified forms of curcumin supplement products it states ‘micelles, liposomes, phospholipid complexes, microemulsions, nano-emulsions, emulsions, solid lipid nanoparticles,

nanostructured lipid carriers, biopolymer nanoparticles and microgels' offer the greatest potential for delivery systems to increase bioavailability. The mechanism is through 'enhancing small intestine permeation, preventing possible degradation in the microenvironment, increasing plasma half-life and enhancing curcumin efficacy'. (Stohs *et al*., 2020).

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

Supplements and reported hepatotoxicity

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

16. Whilst the AFSCA stated that "the exact source of contamination had not yet been established", an update from Italy's National Institute of Health indicated that "the interdisciplinary group, section for dietetics and nutrition of the Technical Committee for animal nutrition and health concluded that, to date, the causes are likely to be related to individual susceptibility, pre-existing alterations, latent hepato-biliary function or even the use of drugs". The Institute did not believe the hepatitis was linked to contamination with heavy metals such as Pb. The Institute adopted a warning for the labelling of the supplements in question (to take effect from 31st December 2019), advising against their use by subjects with altered hepato-biliary function, and recommending medical advice when other medications are being taken. The Institute added that for turmeric powder, which was implicated in one hepatitis

case, no particular recommendations were needed, especially considering its history of consumption as a food.

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

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

Toxicokinetics

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

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

21. Furthermore, it is also reported that the low bioavailability of curcuminoids is due to low membrane transfer and hence low absorption. The underlying mechanisms are an active efflux by P-glycoprotein (pGP) and inter-molecular interactions (Heger et al., 2014; Jamwal, 2018; Ji et al., 2016). Curcumin is reported to act as an inhibitor of pGP, both in function and expression (at the protein and mRNA level) (Lopes-Rodrigues et al., 2016). Overall, the low bioavailability of curcuminoids can be attributed to a number of factors including rapid metabolism (Tullberg *et al*., 2004), efflux transport and low cellular transfer.

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

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

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

membrane crossing, such as curcuminoids, can subsequently be better absorbed. Piperine may also directly increase the intestinal absorptive surface due to the induction of the synthesis of proteins associated with cytoskeletal function of the epithelial cells of the intestine (Khajuria *et al*., 2002). However, the relevance of the findings from this last paper are highly questionable because of the use of high doses and the small changes reported.

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

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

27. A study by Khajeh *et al*., (2023) investigated the effects of pepper on curcumin bioavailability. Black pepper co-administration increased the average curcumin half-life from 2.2 to 4.5 hours and significantly increased urinary average excretion concentration of curcumin at 24 hours (49 vs 218 µg). The authors concluded that the "study indicates that piperine significantly increased CCM [curcumin] oral absorption, reduced systemic clearance, and improved bioavailability." However, this study is only described as a pilot study and is based upon 3 individuals only.

28. Thanawala *et al*., (2023) compared the pharmacokinetics of oral curcuminoids with and without piperine co-formulation. The trial was conducted in 16 healthy fasted male volunteers and curcuminoids were detected in plasma at up to 24 hours using an LC-MS method. Cmax and AUC 0-24h were determined, and the study concluded that “The test formulation WDTE60N [i.e., including piperine] showed improved relative absorption and equivalent exposure at a 10-fold-lower dose of actives than the reference formulation CPC.” It should be noted that the authors of this research in the Journal of Alternative Therapies in Health and Medicine all work for nutraceutical companies.

29. There is evidence that piperine may have less of an effect on bioavailability as an adjuvant compound than reported in some studies. Fanca-Berthon *et al.,* (2021) undertook a study using a cohort of 30 human volunteers assessing several different curcumin supplement delivery mechanisms. The piperine-curcuminoid dose combination included approximately 15 mg of piperine with 1,500 mg of curcuminoids. The study monitored blood plasma concentrations over a 24-hour period after a single dose and included metabolites of curcuminoids as well as the parent compounds curcumin, BDMC and DMC to provide a ‘total curcuminoids’ blood plasma concentration. The piperine-curcuminoid combination did not show any significant differences to the curcuminoid only standard extract, contrary to the Shoba *et al.*, (1998) human study (Fança-Berthon et al., 2021).

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

- The Shoba study had only 8 study participants compared to 30 in the Fanca-Berthon *et al.* study.

- Shoba *et al.* studied a shorter kinetic duration, sampling for only 6 hours compared to 24 hours in the Fanca-Berthon study, which found a Tmax of 6 hours for the parent curcuminoid compounds.

- Shoba *et al.* only measured the single compound curcumin, compared to the metabolites and other related curcuminoids analysed in the Fanca-Berthon study and used for their conclusions, which state: ‘Based on the individual quantification of 15 curcuminoid metabolites, this study demonstrated that unconjugated curcumin, DMC, and BDMC represented only 1% of the total plasma curcuminoids following oral administration of a variety of turmeric formulations. Curcumin plasma concentration alone only reached a maximum of 18 – 21.5 ng/mL in contrast to >400 ng/mL for all metabolites combined.’

31. Some of these criticisms apply to the most recent studies Khajeh et al, 2023; Thanawala et al, 2023), particularly with respect to the range of compounds analysed.

32. There is a lack of any further studies providing direct evidence of piperine enhancing the bioavailability of curcumin in humans. Mimica *et al*., (2022) recently reviewed clinical studies on curcumin, and although piperine was used in a substantial number of them, there was no comparison of its effect on bioavailability. It appears that most studies rely on the findings of Shoba *et al*., (1998). However, there are several examples of piperine being used to aid the bioavailability of other compounds in humans and rodents. The maximum increase in bio-availability observed was approximately 2-fold (Bano *et al*., 1991; Di *et al*., 2015; Lambert *et al*., 2004).

33. 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 increase 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).

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

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

Toxicity

Establishment of a Health Based Guidance Value

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

36. In 1995, JECFA evaluated the results of toxicology and carcinogenicity studies in rats and mice administered turmeric oleoresin containing 79-85 % curcuminoids conducted by the National Toxicology Program (NTP, 1993). After 15 months of treatment, absolute and relative liver weights were increased in both male and female mice in the mid- and highest-dose groups relative to controls. The No Observed Adverse Effect Level (NOAEL) for liver enlargement was 2000 mg/kg in the diet, equal to 220 mg/kg bw/day. On the basis of this NOAEL and a safety factor of 200, JECFA increased its temporary ADI for curcumin to 0-1 mg/ kg bw and extended it, pending the submission of the results of a reproductive toxicity study with curcumin, to be reviewed in 1998 (FAO/WHO, 1995).

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

38. In this study, Wistar rats were fed diets containing curcumin (> 90 % purity) at doses equal to 0, 130-140, 250-290 and 850-960 mg/kg bw/day in

males, and 0, 160, 310-320 and 1000-1100 mg/kg bw/day in females. The total period of treatment was 21 weeks for the parental generation and 24 weeks for the F1 generation. No treatment-related clinical signs of toxicity during the study were reported. Significant decreases in the average weights of the F2 generation pups were observed at days 1 and 7 at the intermediate dose, and on days 7, 14 and 21 at the high dose. These decreases represented < 10 % of the average weight of the concurrent controls and were reported to be within the range of the historical control data. There were no other effects on general health, body weight, pup survival or fertility indices in either generation. JECFA considered the effect on pup weight seen at the intermediate dose (equal to 250-320 mg/kg bw/day) to be incidental and this dose was therefore a NOAEL (FAO/WHO, 2004).

39. In 2010, based on the study used by JECFA in 2004, 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 up to several months. For dose levels up to 12,000 mg/day, only short-term and semi-chronic (sic) adverse effects, such as gastrointestinal effects, headache and rash were observed, but without a clear dose-relationship.

40. In the meeting of the COT on 10th March 2020, Members questioned the relevance of comparing exposures from supplement intake to the ADI for dietary curcumin. It was decided that it would not be appropriate because synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered TK profiles and increased bioavailability. Thus, the levels determined as of low safety concern in food may not be relevant for supplements.

Hepatitis and idiosyncratic drug hepatotoxicity

41. 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 signs of hepatitis are often non-specific but in the later stages of the disease the signs 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 signs such as bruising secondary to lack of clotting factors, encephalopathy caused by failure to convert ammonia to urea, and itching when bile salts are deposited in the skin instead of being eliminated in the bile. The liver has a remarkable ability to regenerate after damage but if the damage continues it can fail to replicate the original complex cellular architecture necessary for normal function and instead produces cirrhosis, a combination of fibrous tissue and regenerative nodules.

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

43. 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 viruses that cause hepatitis can be identified either by demonstrating an antigenic part of the virus or a specific antibody response to the virus in the blood. Autoimmune disease can be diagnosed from the pattern of antibodies to specific cellular components such as from the mitochondria or nuclei and from the clinical picture of other organ involvement. Damaged liver cells tend to leak enzymes into the blood and

some clue as to the site of greatest damage within the liver can be gleaned from the pattern of these enzymes with transaminases, particularly alanine aminotransferase (ALT), being released from damaged parenchymal cells and alkaline phosphatase (ALP) being released from cells lining the bile ducts.

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

45. The defining feature of active chronic hepatitis is infiltration of lymphocytes from portal tracts with associated death of liver cells, so called interface hepatitis. This, in time, is associated with fibrosis. Sometimes the amount of inflammation is less, and a biopsy fails to show interface hepatitis. The presence of plasma cells or discrete lymphoid aggregates may suggest a viral cause. Some storage disorders, for example Wilson’s disease and copper accumulation, and alpha 1 antitrypsin deficiency, show morphological evidence of a chronic active hepatitis. (Ferrell, 2000).

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

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

Curcuminoids and hepatotoxicity

48. Full details of the relevant animal and human studies are summarised in Annex A.

49. 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.

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

51. Between December 2018 and 20th July 2019, a total of 21 individual cases of acute cholestatic hepatitis "likely to be linked to the consumption of

food supplements based on curcumin and piperine" were reported on Italian territory. A total of 18 different turmeric supplements have been associated with this hepatitis outbreak, one of which ("Curcuma Liposomal & black pepper" by Nutrimea) was recalled by Belgium's Federal Agency for Food Chain Safety (AFSCA) (Chu, W, 2019).

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

53. ANSES report that their 'nutrivigilance scheme" has received over 100 reports of adverse effects, including 15 reports of hepatitis, potentially related to the consumption of food supplements containing turmeric or curcumin'. This has led the French agency to provide a recent opinion, in June 2022, on turmeric safety (ANSES, 2022). In their opinion, ANSES advises against 'the consumption of food supplements containing turmeric by people with bile duct disease' and that 'there is a risk of curcumin interacting with certain medications such as anticoagulants, cancer drugs and immunosuppressants.'

54. Pancholi *et al.*, (2021) dispute the potential hepatoxic effects reported in human studies. They state that only a handful of human cases reporting toxic symptoms, out of millions of humans exposed to curcuminoid supplements daily, is not a significant finding, with those that have symptoms having other personal reasons for these. However, it should be noted that 3 of the authors of the Pancholi *et al.*, (2021) publication are employed by a supplements company which funded the study, with little new evidence provided against the possible idiosyncratic effects of curcuminoids.

Medium to long term safety of curcuminoids

55. 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, ALP, gamma-glutamyl transferase (GGT) and bilirubin were all within the normal range after the 90-day exposure, indicating no liver effects during this time. Little new evidence was provided on the possible idiosyncratic effects of curcuminoids.

56. 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).

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

58. 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.

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

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

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

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

62. The EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment of Pb exposure. The respective BMDLs derived from blood Pb levels in µg/L (corresponding dietary intake values in µg/kg bw/d) were: developmental neurotoxicity $BMDL_{01}$, 12 (0.50); increased systolic blood pressure (SBP) $BMDL_{01}$, 36 (1.50); increased prevalence of chronic kidney disease $BMDL_{10}$, 15 (0.63). The Panel highlighted that by protecting children, who are 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).

63. After review of the EFSA CONTAM (2010) and JECFA 2011 (FAO/WHO, 2011) evaluations, the COT (COT, 2013) agreed that neurodevelopmental effects of Pb represent the most sensitive endpoint, whilst also being protective of the other toxicological end points. In their assessment of 2013, the Committee concluded that a Margin of Exposure (MOE) of > 1 can be taken to imply that at most, any risk is likely to be small. MOEs < 1 do not necessarily indicate a problem, but scientific uncertainties mean that a material risk cannot be ruled out. This applies particularly when MOEs are substantially < 1.

Contamination with other potential adulterants

C.zedoaria

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

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

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

Azo dyes

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

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

68. The German Federal Institute for Risk Assessment (BfR, 2003) concluded that for the Sudan dyes, given their potential genotoxic mechanism

of action, a concentration cannot be determined for these chemical compounds at which a carcinogenic action does not occur (the ‘threshold value’). Therefore, the BfR could not propose a tolerable daily intake (TDI) for the Sudan dyes.

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

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

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

72. In EFSA’s 2005 evaluation, on consideration of Metanil yellow the Panel stated that there was indication of genotoxic activity however concluded there was “some indication of tumour promoting activity but probably only through enzyme induction.” (EFSA, 2005)

73. In 2017 JECFA evaluated the yellow azo dyes Quinoline Yellow and D&C Yellow No. 10. They concluded that due to their similar chemical structures and manufacturing process that it would be acceptable to take the toxicology data for D&C Yellow No. 10 to support conclusions for Quinoline Yellow. Considering the two similar long-term studies on D&C Yellow No. 10 in Sprague Dawley rats (Hogan, G.K. and Knezevich, A.L., 1982a, 1982b) a dietary NOAEL of 0.5% (equivalent to 250 mg/kg bw per day), based on effects on body and organ weights was identified. Using this NOAEL and an uncertainty factor of 100, JECFA established an ADI of 0 – 3 mg/kg bw for Quinoline Yellow (FAO/WHO, 2017).

Exposure assessment

Dietary exposure

74. Curcumin powder is authorised for use as a colouring agent in food (E 100), where its purity is specified as “not less than 90% total colouring matters” (i.e. curcumin, DMC, and BDMC) (EC, 2008). Assimilated additives legislation 1333/2008 sets out the maximum permitted levels (MPLs) for E 100 in foodstuffs as 500 mg/kg (total limit in combination with other group III additives; see Annex 2 and 3 of assimilated additives legislation 1333/2008) depending on the food item and beverages (which range from 100 to 200 mg/L) (EC, 1994).

75. EFSA have assessed the exposure to curcumin through the diet in 2010 and again in 2014. In their 2010 assessment, EFSA used the UK NDNS data to estimate dietary curcumin exposure in the adult population in the UK, and the NDNS (UK) and EXPOCHI (other EU countries) data to estimate the exposure in children (1.5 – 4.5 and 1 – 10-year-olds, respectively). Based on maximum permitted levels, for adults, mean estimated exposure was 0.8 mg/kg bw/day, which is within the JECFA 2004 ADI of 0 - 3 mg/kg bw (FAO/WHO, 2004a). For children, mean estimated exposures ranged from within to slightly above the upper bound of the ADI (0.5 – 3.8 mg/kg bw/day). There were some slight exceedances of the ADI in children regardless of

whether MPLs or maximum reported use levels were used to estimate exposure.

76. Considering the estimated exceedances of the dietary ADI by 1 – 10-year-old children at the mean and high level, EFSA (2014) conducted a refined exposure assessment for curcumin. This refined exposure assessment considered additional information on the consumption of curcumin-containing foods gathered from the EFSA Comprehensive European Food Consumption Database. Each age category was contributed to by a range of countries, and consumption by the UK population was represented only in the “adult” category (18 – 60-years-old). Additional information on use levels was also obtained from Member States.

77. Using the additional information, the refined assessment (EFSA, 2014) estimated lower intakes of curcumin for both adults and the elderly (no UK estimate) than the 2010 assessment. Exposures for adolescents (no UK estimate), adults, and the elderly (no UK estimate) were below the ADI at the mean and high level (97.5th percentile). Estimated exposures were also lower for children (no UK estimate) and toddlers (no UK estimate) at the mean and high levels, although some high-level estimates were close to the upper bound of the ADI and slight exceedances were observed in one (non-UK) survey for each age group. More details of EFSA ANS Panel’s (2010; 2014) curcumin exposure assessments are presented in Annex B.

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

Exposure through turmeric supplements

79. In addition to exposure to curcumin through a normal diet, turmeric supplements can also be taken. These can be bought as 'over the counter' supplements or by 'self-dosing', through consumption of spices in large quantities. The exposures for curcumin and heavy metals from supplements have been calculated using data from a recent survey by Fera (Fera Science Ltd, 2022) and are described in paragraphs 83 – 89.

80. 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). Assimilated regulation 231/2012 sets out a different list of permitted solvents: ethyl acetate, acetone, n-butanol, methanol, ethanol, hexane, propan-2-ol, and dichloromethane. Residual solvent concentrations must not exceed more than 50 mg/kg, singly or in combination, except for dichloromethane which has a residual concentration maximum level of 10 mg/kg. The legislation also states that CO_2 may also be used as an extraction solvent and for which no maximum residual level is specified (EC, 2012). The extraction methodology used affects the curcuminoid content (37-55 %) (Li, *et al*., 2011), and the essential oil content (< 25%) (Braga *et al*., 2003) of the turmeric oleoresin.

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

82. Curcumin powder can be obtained through the purification of turmeric oleoresin by crystallisation (Li *et al.,* 2011). However, there is limited commercial availability of authentic samples of pure curcumin, since its separation from DMC and BDMC can be difficult and time consuming. Thus, commercial "pure" curcumin is, in many cases, a mixture of at least these

three curcuminoids (Li *et al*., 2011). For example, a sample of commercial "pure" curcumin (labelled as 94% purity) was, after HPLC analysis, found to have approximately 70% purity of curcumin (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).

83. As mentioned earlier in this statement and described in paragraphs 23 - 31, in supplements it is common practice to alter the curcumin product in an effort to change its metabolism and enhance its bioavailability, by addressing the metabolism, membrane transfer or both. Methods used for this include the use of liposomal curcumin, nanoparticle dispersion, the use of curcumin phospholipid complex and the use of structural analogues of curcumin that are water soluble.

Assessment after 2021 sample survey - Curcuminoids

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

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

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

87. 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.

88. From the survey, taking the recommended doses daily according to the supplement's label, would result in exposure levels for a 70 kg adult ranging from 0.1 to 7 mg/kg bw/day (mean of 1.7 mg/kg bw/day). Two of the 15 supplement samples would lead to exposures above the dietary ADI of 0 - 3 mg/kg bw. Taking the supplement that provides 7 mg/kg bw/day for a 70 kg adult, would contribute a further approximate 3-fold exposure to curcuminoids than would be expected from a high dietary exposure (2.6 mg/kg bw/day, see Table 2 in Annex B).

89. 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.

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

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

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

92. 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

assimilated EU legislation EC No. 1881/2006 or below the EU ML set for root spices by the amendment EU 2021/1317 (due to the recent date, this amendment to the EU regulation is not in UK legislation). For supplements, the MLs are 3 mg/kg for Pb, 1 mg/kg for Cd and 0.1 mg/kg for Hg. For root spice powders the EU ML is 1.5 mg/kg for Pb. Arsenic does not have a ML set for supplements, but all concentrations, bar two samples at 0.45 and 0.29 mg/kg, were below the 0.2 mg/kg ML set for white rice by EU 2015/1006.

93. One sample, a turmeric spice powder, contained a Pb concentration approximately 10 times higher than the majority of other samples analysed, at 2.25 mg/kg. This would be over the amended recent EU ML of 1.5 mg/kg for root spice powders. This sample also had the second highest concentration of chromium (Cr) at 2.11 mg/kg, which may indicate adulteration with lead chromate. If this sample were taken as a supplement at, for example, a teaspoon per day (4g) the total exposure to lead from this source alone would be 0.13 µg/kg bw/day for a 70 kg adult. This is approximately 25% of the estimated dietary exposure of 0.5 µg/kg bw day, equivalent to the $BMDL_{01}$ of 12 µg/L blood Pb concentration, for effects of Pb on developmental neurotoxicity (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010), i.e. MOE of 3.8. As this is greater than 1, it would suggest that in itself any risk from such exposure to Pb is likely to be small. but may be of significance when added to other sources of Pb exposure.

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

95. On evaluation of the other trace elements from the 30 samples, results that differed by greater than the mean plus 2 x the standard deviation and 5 x the mean of that sample type (i.e., fresh, powder or supplement) are summarised in Tables 4 and 5 in Annex B. If the supplements are taken as described on their labels, no estimated exposures for any trace elements

would exceed any health-based guidance values (HBGVs), where HBGVs exist.

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

a) the different geographical sources of the products and therefore the differing background trace element concentrations in the environments from which the products were derived

b) the varying chemical nature of the different supplement formulations

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

Exposure to other potential adulterants

C.zedoaria

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

Azo dyes

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

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

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

102. From a recent FSA survey of 30 turmeric spice products (this included 6 non-branded products) in 2022, no illegal dyes were detected, although this did not include analysis for the Sudan red dyes or Metanil yellow. In 2023, the FSA commissioned a further 21 turmeric spice powder sample analyses for illegal dyes (method included Sudan red dyes but did not include Metanil yellow), with all samples negative.

Risk Characterisation

Curcuminoids

103. Consumption as part of the normal diet (from its use as an additive and spice) would lead to curcumin exposures that are generally within the ADI

of 0 - 3 mg/kg bw, although at the upper end of the exposure range there may be a slight exceedance of the ADI, particularly for younger consumers.

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

105. With regard to dietary turmeric supplements, a recent 2021 survey shows that a small proportion (2 from 15 samples) of the tested products would lead to high exposure of curcuminoids i.e. exposures at or above the ADI of 0 - 3 mg/kg bw. The COT concluded from previous discussions that this ADI may not be appropriate for supplements. This is because as also shown in the 2021 survey, 10 of the 15 supplements analysed contained piperine or may be otherwise formulated to increase the bioavailability of curcumin from that of the natural form. The resulting changes in the TK of the curcuminoids could potentially increase the hepatotoxicity. After a review of the current evidence, it is concluded that the claim with many supplements that piperine improves the bioavailability of curcuminoids is questionable with high uncertainty. There is very limited scientific evidence for the claimed benefits of the inclusion of piperine.

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

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

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

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

Contamination of raw, ground turmeric and curcumin supplements

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

111. After the Italian incident in 2018 and 2019 (see paragraphs 15 to 17), Italy's National Institute of Health concluded that a contaminant was unlikely to be the underlying cause. Furthermore, the recent 2021 FSA-funded survey of 30 turmeric products and the 2022 survey of 70 turmeric spice powder products did not show concentrations of Pb in any of the samples above the ML of 3 mg/kg for supplements, and in only one spice powder sample, which had a Pb concentration at 2.25 mg/kg, above a recent ML set by the EU of 1.5 mg/kg. These data add to the evidence base that the hepatotoxic effects

associated with taking turmeric are more likely due to the curcuminoids than heavy metal contamination. In addition, the clinical picture is not that typically observed following Pb exposure. Therefore, it is concluded that after the results of the recent product surveys, Pb contamination of turmeric products is likely not the reason for incidents such as the hepatoxicity reported in the Italian cases. However, it is still uncertain why this incident occurred as a cluster of cases.

112. On evaluation of the other trace element concentrations from the recent study by Fera Science Ltd (Fera Science Ltd, 2022), the metal concentrations across all of the products tested were extremely variable. This can be attributed to the geographical variation of the source of the products, and/or the other varying additives within supplements. Concentrations of trace elements (metals) that are relatively higher than the average across that product type have been presented in Annex B to this statement. However, no calculated exposures for any trace elements, if taking the supplements as described on their labels, would exceed any HBGVs, where HBGVs exist.

Summary and conclusions

113. 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.

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

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

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

117. 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 within the dietary ADI using the 2010 and the 2014 EFSA dietary exposures. However, when consumed in high quantities such as for its purported health benefits, or via the intake of supplements, occasional exceedances of the ADI can occur. In a recent curcuminoid survey of 15 supplements, when following the dosage advice on the label, 2 of these would lead to exposures above the ADI. It is concluded that if consumption was based on the label guidance there may be minor exceedances of the dietary ADI, but this should not pose a significant risk to the population.

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

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

possibility of an unexpected idiosyncratic response should be considered when providing guidance on the use of such supplements.

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

121. Other ‘novel’ supplement types such as micellar, nano, and micro formulations should be assessed in further detail, with regard to their pharmacokinetics and therefore their impact on curcuminoid bioavailability. This is an area of particular concern. This further detail is requested regardless that they only make up a likely small percentage of the supplement market at present, as they may become more popular in the future.

Statement Number COT/2024/07

December 2024

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
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
As	Arsenic
BDMC	Bisdemethoxycurcumin
BfR	German Federal Institute for Risk Assessment
BMDL	Benchmark Dose Lower Confidence Level
CCM	Curcumin
Cd	Cadmium
CO_2	Carbon Dioxide
CONTAM Panel	Scientific Panel on Contaminants in the Food Chain
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Cr	Chromium
DILIN	United States Drug-Induced Liver Injury Network
DMC	Desmethoxycurcumin
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
EXPOCHI	Exposure Assessments For Children In Europe
FAO	Food and Agricultural Organisations of the United Nations
GD	Gestation Day
GGT	Gamma-Glutamyl Transferase

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

References

Alok, A., Singh, I.D., Singh, S., Kishore, M., Jha, P.C., 2015. Curcumin – Pharmacological Actions And its Role in Oral Submucous Fibrosis: A Review. J Clin Diagn Res 9, ZE01–ZE03. JCDR - Antioxidant, Fibrinolytic property, Herbal medicine, Nanoparticles, Turmeric

Amalraj, A., Varma, K., Jacob, J., Kuttappan, S., 2021. Efficacy and safety of a gut health product (Actbiome) prepared by incorporation of asafoetida-curcumin complex onto the turmeric dietary fiber in the management of gut health and intestinal microflora in healthy subjects: A randomized, double-blind, placebo controlled study. Bioactive Carbohydrates and Dietary Fibre 26, 100280. https://doi.org/10.1016/j.bcdf.2021.100280

American Academy of Allergy Asthma & Immunology, 2020. Medications and Drug Allergic Reactions. Medications and Drug Allergic Reactions AAAAI

Ammon, H.P., Wahl, M.A., 1991. Pharmacology of Curcuma longa. Planta Med 57, 1–7. Thieme E-Journals - Planta Medica / Abstract

ANSES (AGENCE NATIONALE DE SÉCURITÉ SANITAIRE de l'alimentation, de l'environnement et du travail), 2022. L'évaluation des risques liés à la consommation de compléments alimentaires contenant du curcuma. AVIS révisé de l'Anses relatif à l'évaluation des risques relatifs à la consommation de compléments alimentaires contenant du curcuma

Apica, B.S., Lee, W.M., 2014. Drug-Induced Liver Injury, in: McManus, L.M., Mitchell, R.N. (Eds.), Pathobiology of Human Disease. Academic Press, San Diego, pp. 1825–1837. https://doi.org/10.1016/B978-0-12-386456-7.04208-8

Appelboom, T., Maes, N., Albert, A., 2014. A New Curcuma Extract (Flexofytol®) in Osteoarthritis: Results from a Belgian Real-Life Experience. Open Rheumatol J 8, 77–81. https://doi.org/10.2174/1874312901408010077

Bano, G., Raina, R.K., Zutshi, U., Bedi, K.L., Johri, R.K., Sharma, S.C., 1991. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. European Journal of Clinical Pharmacology 41, 615–617. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers European Journal of Clinical Pharmacology Springer Nature Link

Bejar Ezra, 2018. Adulteration of turmeric (Curcuma longa) root and rhizome, and root and rhizome extracts. Botanical Adulterants Bulletin, 2018 (abstract only).

BfR (Federal Institute for Risk Assessment), 2003. Dyes Sudan I to IV in food. WHO_TRS_859.pdf

Braga, M.E.M., Leal, P.F., Carvalho, J.E., Meireles, M.A.A., 2003. Comparison of Yield, Composition, and Antioxidant Activity of Turmeric (Curcuma longa L.) Extracts Obtained Using Various Techniques. J. Agric. Food Chem. 51, 6604–6611. Comparison of Yield, Composition, and Antioxidant Activity of Turmeric (Curcuma longa L.) Extracts Obtained Using Various Techniques Journal of Agricultural and Food Chemistry ACS Publications

Chavalittumrong, P., Chivapat, S., Rattanajarasroj, S., Punyamong, S., Chuthaputti, A., Phisalaphong, C., 2002. Chronic toxicity study of curcuminoids in rats. The Songklanakarin Journal of Science and Technology 24, 16.

Chen, S., Li, Q., McClements, D.J., Han, Y., Dai, L., Mao, L., Gao, Y., 2020. Co-delivery of curcumin and piperine in zein-carrageenan core-shell nanoparticles: Formation, structure, stability and in vitro gastrointestinal digestion. Food Hydrocolloids 99, 105334. https://doi.org/10.1016/j.foodhyd.2019.105334

Chu, W, 2019. Belgium recall same curcumin-based supplement linked to Italian hepatitis cases. Belgium recall same curcumin-based supplement linked to Italian hepatitis cases

COT, 2013. Statement on the potential risks from lead in the infant diet. [ARCHIVED CONTENT] COT statement on lead Food Standards Agency

Cowell, W., Ireland, T., Vorhees, D., Heiger-Bernays, W., 2017. Ground Turmeric as a Source of Lead Exposure in the United States. Public Health Rep 132, 289–293. Ground Turmeric as a Source of Lead Exposure in the United States - Whitney Cowell, Thomas Ireland, Donna Vorhees, Wendy Heiger-Bernays, 2017

Daniells, S, 2022. Italy prohibits all health claims linked to turmeric, issues warning for labels. Italy prohibits all health claims linked to turmeric, issues warning for labels

Dhakal, S., Schmidt, W.F., Kim, M., Tang, X., Peng, Y., Chao, K., 2019. Detection of Additives and Chemical Contaminants in Turmeric Powder Using FT-IR Spectroscopy. Foods 8, E143. https://doi.org/10.3390/foods8050143

Dhanya, K., Syamkumar, S., Siju, S., Sasikumar, B., 2011. Sequence characterized amplified region markers: A reliable tool for adulterant detection in turmeric powder. Food Research International 44, 2889–2895. https://doi.org/10.1016/j.foodres.2011.06.040

Di, X., Wang, X., Di, X., Liu, Y., 2015. Effect of piperine on the bioavailability and pharmacokinetics of emodin in rats. Journal of Pharmaceutical and Biomedical Analysis 115, 144–149. https://doi.org/10.1016/j.jpba.2015.06.027

Dixit, S., Khanna, S.K., Das, M., 2008. ASimple 2-Directional High-Performance Thin-Layer Chromatographic Method for the Simultaneous Determination of Curcumin, Metanil Yellow, and Sudan Dyes in Turmeric,

Chili, and Curry Powders. Journal of AOAC INTERNATIONAL 91, 1387–1396. https://doi.org/10.1093/jaoac/91.6.1387

Dixit, S., Purshottam, S.K., Khanna, S.K., Das, M., 2009. Surveillance of the quality of turmeric powders from city markets of India on the basis of curcumin content and the presence of extraneous colours. Food Additives & Contaminants: Part A 26, 1227–1231. https://doi.org/10.1080/02652030903016586

EC, 2008. Commission Directive 2008/128/EC of 22 December 2008 laying down specific purity criteria concerning colours for use in foodstuffs (Codified version) (Text with EEA relevance), OJ L. Directive - 2008/128 - EN - EUR-Lex

EC, 1994. EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE 94/36/EC of 30 June 1994 on colours for use in foodstuffs. eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31994L0036&from=EN

EFSA, 2005. Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) to review the toxicology of a number of dyes illegally present in food in the EU. EFSA Journal. https://doi.org/10.2903/j.efsa.2005.263

EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010. Scientific Opinion on Lead in Food. EFS2 8. https://doi.org/10.2903/j.efsa.2010.1570

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010. Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive. EFS2 8. https://doi.org/10.2903/j.efsa.2010.1679

EFSA, 2014. Refined exposure assessment for curcumin (E 100). EFSA Journal, 12:10, 3876. https://doi.org/10.2903/j.efsa.2014.3876

Fança-Berthon, P., Tenon, M., Bouter-Banon, S.L., Manfré, A., Maudet, C., Dion, A., Chevallier, H., Laval, J., van Breemen, R.B., 2021. Pharmacokinetics of a Single Dose of Turmeric Curcuminoids Depends on Formulation: Results of a Human Crossover Study. The Journal of Nutrition 151, 1802–1816. https://doi.org/10.1093/jn/nxab087

FAO/WHO, 1995. Evaluation of certain food additives and naturally occurring toxicants (Fourty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 859.

FAO/WHO, 2004a. Evaluation of certain food additives and contaminants. Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 922. IRIS Home

FAO/WHO, 2004b. Curcumin Chemical and Technical Assessment. Microsoft Word - 2004-02-24 CTA 61 Curcumin.doc

FAO/WHO, 2017. Safety evaluation of certain food additives: prepared by the eighty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva. Safety evaluation of certain food additives: prepared by the eighty-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

FAO/WHO, 2011. Safety evaluation of certain food additives and contaminants, The 74th Meeting of the Joint FAO WHO Expert Committee on Food Additives. WHO, Geneva. Compendium of Food Additive Specifications - Joint FAO/WHO Expert Committee on Food Additives (JECFA) 74th Meeting 2011. FAO JECFA Monographs 11

Fera Science Ltd, 2022. Turmeric survey for the FSA (FS430403). Turmeric Survey Published in FSA Research and Evidence

Ferrell, L., 2000. Liver Pathology: Cirrhosis, Hepatitis, and Primary Liver Tumors. Update and Diagnostic Problems. Mod. Pathol. 13, 679–704. https://doi.org/10.1038/modpathol.3880119

Forsyth, J.E., Nurunnahar, S., Islam, S.S., Baker, M., Yeasmin, D., Islam, M.S., Rahman, M., Fendorf, S., Ardoin, N.M., Winch, P.J., Luby, S.P., 2019. Turmeric means “yellow” in Bengali: Lead chromate pigments added to turmeric threaten public health across Bangladesh. Environmental Research 179, 108722. https://doi.org/10.1016/j.envres.2019.108722

Funk, J.L., Frye, J.B., Oyarzo, J.N., Zhang, H., Timmermann, B.N., 2010. Anti-Arthritic Effects and Toxicity of the Essential Oils of Turmeric (Curcuma longa L.). J Agric Food Chem 58, 842–849. https://doi.org/10.1021/jf9027206

Grand View Research (2022). Curcumin Market Size, Share & Trends Report By Application (Pharmaceutical, Food, Cosmetics), By Region (North America, Europe, Asia Pacific, CSA, MEA), And Segment Forecasts, 2020 - 2028. Curcumin Market Size & Share Analysis Report, 2028

Gupta, S.C., Patchva, S., Aggarwal, B.B., 2012. Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials. AAPS J 15, 195–218. https://doi.org/10.1208/s12248-012-9432-8

Halegoua-DeMarzio, D., Navarro, V., Ahmad, J., Avula, B., Barnhart, H., Barritt, A.S., Bonkovsky, H.L., Fontana, R.J., Ghabril, M.S., Hoofnagle, J.H., Khan, I.A., Kleiner, D.E., Phillips, E., Stolz, A., Vuppalanchi, R., 2022. Liver Injury Associated with Turmeric–a Growing Problem: Ten Cases from the Drug-Induced Liver Injury Network [DILIN]. The American Journal of Medicine. https://doi.org/10.1016/j.amjmed.2022.09.026

Haroyan, A., Mukuchyan, V., Mkrtchyan, N., Minasyan, N., Gasparyan, S., Sargsyan, A., Narimanyan, M., Hovhannisyan, A., 2018. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. BMC

Complementary and Alternative Medicine 18, 7. https://doi.org/10.1186/s12906-017-2062-z

He, Y., Li, W., Hu, G., Sun, H., Kong, Q., 2018. Bioactivities of EF24, a Novel Curcumin Analog: A Review. Frontiers in Oncology 8. Frontiers Bioactivities of EF24, a Novel Curcumin Analog: A Review

Heger, M., Golen, R.F. van, Broekgaarden, M., Michel, M.C., 2014. The Molecular Basis for the Pharmacokinetics and Pharmacodynamics of Curcumin and Its Metabolites in Relation to Cancer. Pharmacol Rev 66, 222–307. https://doi.org/10.1124/pr.110.004044

Hogan, G.K. and Knezevich, A.L., 1982a. Long-term dietary toxicity/carcinogenicity study of D&C Yellow #10 in rats. Bio/dynamics Inc. Project no. 77-1884. Submitted by International Association of Color Manufacturers (IACM) to WHO, January 2016.

Hogan, G.K. and Knezevich, A.L., 1982b. Long-term dietary toxicity/carcinogenicity study of D&C Yellow #10 in rats, Bio/dynamics Inc. Project No. 78-2163. Submitted by International Association of Color Manufacturers (IACM) to WHO, January 2016.

Ireson, C.R., Jones, D.J.L., Orr, S., Coughtrie, M.W.H., Boocock, D.J., Williams, M.L., Farmer, P.B., Steward, W.P., Gescher, A.J., 2002. Metabolism of the Cancer Chemopreventive Agent Curcumin in Human and Rat Intestine. Cancer Epidemiol Biomarkers Prev 11, 105–111.

Jamwal, R., 2018. Bioavailable curcumin formulations: A review of pharmacokinetic studies in healthy volunteers. Journal of Integrative Medicine 16, 367–374. https://doi.org/10.1016/j.joim.2018.07.001

Ji, H., Tang, J., Li, M., Ren, J., Zheng, N., Wu, L., 2016. Curcumin-loaded solid lipid nanoparticles with Brij78 and TPGS improved in vivo oral

bioavailability and in situ intestinal absorption of curcumin. Drug Delivery 23, 459–470. https://doi.org/10.3109/10717544.2014.918677

Joober, R., Schmitz, N., Annable, L., Boksa, P., 2012. Publication bias: What are the challenges and can they be overcome? J Psychiatry Neurosci 37, 149–152. https://doi.org/10.1503/jpn.120065

Khajeh Pour, S., Blanton, C., Ghimire, B., Aghazadeh-Habashi, A., 2023. Development of a rapid, sensitive, and selective LC-MS/MS method for quantifying curcumin levels in healthy human urine: Effect of pepper on curcumin bioavailability. Food Sci Nutr 11, 7732–7741. https://doi.org/10.1002/fsn3.3691

Kanai, M., Yoshimura, K., Asada, M., Imaizumi, A., Suzuki, C., Matsumoto, S., Nishimura, T., Mori, Y., Masui, T., Kawaguchi, Y., Yanagihara, K., Yazumi, S., Chiba, T., Guha, S., Aggarwal, B.B., 2011. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer Chemother Pharmacol 68, 157–164. https://doi.org/10.1007/s00280-010-1470-2

Kaplowitz, N., 2005. Idiosyncratic drug hepatotoxicity. Nat Rev Drug Discov 4, 489–499. https://doi.org/10.1038/nrd1750

Khajuria, A., Thusu, N., Zutshi, U., 2002. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: Influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. Phytomedicine 9, 224–231. https://doi.org/10.1078/0944-7113-00114

Lakshmi, S., Padmaja, G., Remani, P., 2011. Antitumour Effects of Isocurcumenol Isolated from Curcuma zedoaria Rhizomes on Human and Murine Cancer Cells. International Journal of Medicinal Chemistry 2011, e253962. https://doi.org/10.1155/2011/253962

Lambert, J.D., Hong, J., Kim, D.H., Mishin, V.M., Yang, C.S., 2004. Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice. J Nutr 134, 1948–1952. https://doi.org/10.1093/jn/134.8.1948

Latif, M.A., Morris, T.R., Miah, A.H., Hewitt, D., Ford, J.E., 1979. Toxicity of shoti (Indian arrowroot: Curcuma zedoaria) for rats and chicks. Br J Nutr 41, 57–63. https://doi.org/10.1079/bjn19790012

Li Shiyou, Yuan Wei, Deng Guangrui, Wang Ping, Yang Peiying,, Aggarwal Bharat, 2011. Chemical Composition and Product Quality Control of Turmeric (Curcuma longa L.). TOPHARMCJ 5, 28–54. https://doi.org/10.2174/2210290601102010028

Liu, Z., Smart, J.D., Pannala, A.S., 2020. Recent developments in formulation design for improving oral bioavailability of curcumin: A review. Journal of Drug Delivery Science and Technology 60, 102082. https://doi.org/10.1016/j.jddst.2020.102082

Lopes-Rodrigues, V., Sousa, E., Vasconcelos, M.H., 2016. Curcumin as a Modulator of P-Glycoprotein in Cancer: Challenges and Perspectives. Pharmaceuticals (Basel) 9, 71. https://doi.org/10.3390/ph9040071

Luber, R.P., Rentsch, C., Lontos, S., Pope, J.D., Aung, A.K., Schneider, H.G., Kemp, W., Roberts, S.K., Majeed, A., 2019. Turmeric Induced Liver Injury: A Report of Two Cases. Case Reports Hepatol 2019, 6741213. https://doi.org/10.1155/2019/6741213

Lukefahr, A.L., McEvoy, S., Alfafara, C., Funk, J.L., 2018. Drug-induced autoimmune hepatitis associated with turmeric dietary supplement use. BMJ Case Reports bcr-2018-224611. https://doi.org/10.1136/bcr-2018-224611

Mimica, B., Bučević Popović, V., Banjari, I., Jeličić Kadić, A., Puljak, L., 2022. Methods Used for Enhancing the Bioavailability of Oral Curcumin in

Randomized Controlled Trials: A Meta-Research Study. Pharmaceuticals 15, 939. https://doi.org/10.3390/ph15080939

Nagaraja, T.N., Desiraju, T., 1993. Effects of chronic consumption of metanil yellow by developing and adult rats on brain regional levels of noradrenaline, dopamine and serotonin, on acetylcholine esterase activity and on operant conditioning. Food and Chemical Toxicology 31, 41–44. https://doi.org/10.1016/0278-6915(93)90177-Z

Nakagawa, Y., Mori, K., Yamada, S., Mukai, S., Hirose, A., Nakamura, R., 2022. The Oral Administration of Highly-Bioavailable Curcumin for One Year Has Clinical and Chondro-Protective Effects: A Randomized, Double-Blinded, Placebo-Controlled Prospective Study. Arthroscopy, Sports Medicine, and Rehabilitation 4, e393–e402. https://doi.org/10.1016/j.asmr.2021.10.016

Nisa, A., Zahra, N., B., Y., 2016. Sudan dyes and their potential health effects. Pakistan Journal of biochemistry and molecular biology 49, 29–35.

Olojede, A.O., Nwokocha, C.C., Akinpelu, A.O., Dalyop, T., 2009. Effect of Variety, Rhizome and Seed Bed Types on Yield of Turmeric (Curcuma longa L) under a Humid Tropical Agro-Ecology 3. Advances in Biological Research 3 (1-2): 40-42. Effect of Variety, Rhizome and Seed Bed Types on Yield of Turmeric (Curcuma longa L) under a Humid Tropical Agro-Ecology.

Pan, H., Feng, J., He, G.-X., Cerniglia, C.E., Chen, H., 2012. Evaluation of impact of exposure of Sudan azo dyes and their metabolites on human intestinal bacteria. Anaerobe 18, 445–453. https://doi.org/10.1016/j.anaerobe.2012.05.002

Pancholi, V., Smina, T.P., Kunnumakkara, A.B., Maliakel, B., Krishnakumar, I.M., 2021. Safety assessment of a highly bioavailable curcumin-galactomannoside complex (CurQfen) in healthy volunteers, with a special reference to the recent hepatotoxic reports of curcumin supplements: A 90-

days prospective study. Toxicology Reports 8, 1255–1264. https://doi.org/10.1016/j.toxrep.2021.06.008

Petracca, M., Quarantelli, M., Moccia, M., Vacca, G., Satelliti, B., D'Ambrosio, G., Carotenuto, A., Ragucci, M., Assogna, F., Capacchione, A., Lanzillo, R., Morra, V.B., 2021. ProspeCtive study to evaluate efficacy, safety and tolerability of dietary supplemeNT of Curcumin (BCM95) in subjects with Active relapsing MultIple Sclerosis treated with subcutaNeous Interferon beta 1a 44 mcg TIW (CONTAIN): A randomized, controlled trial. Multiple Sclerosis and Related Disorders 56, 103274. https://doi.org/10.1016/j.msard.2021.103274

Pfeiffer, E., Höhle, S., Solyom, A.M., Metzler, M., 2003. Studies on the stability of turmeric constituents. Journal of Food Engineering 56, 257–259.

Rao, S.N., Vennapusa, C.S.R., Patel, S., Meti, S., Huggar, B., 2021. Determination of banned adulterants in turmeric and chilli powders using ultra-high-performance liquid chromatography. Journal of Liquid Chromatography & Related Technologies 44, 235–243. https://doi.org/10.1080/10826076.2021.1891933

Ravindranath, V., Chandrasekhara, N., 1981. Metabolism of curcumin--studies with [3H]curcumin. Toxicology 22, 337–344. https://doi.org/10.1016/0300-483x(81)90027-5

Sasikumar, B., 2019. Advances in adulteration and authenticity testing of turmeric (Curcuma longa L.). J Spices Arom Crops 96–105. https://doi.org/10.25081/josac.2019.v28.i2.6072

Sasikumar, B., 2005. Genetic resources of Curcuma: diversity, characterization and utilization. Plant Genetic Resources 3, 230–251. https://doi.org/10.1079/PGR200574

Sasikumar, B., Syamkumar, S., Remya, R., John Zachariah, T., 2004. PCR Based Detection of Adulteration in the Market Samples of Turmeric Powder. Food Biotechnology 18, 299–306. https://doi.org/10.1081/FBT-200035022

Saxena, B., Sharma, S., 2015. Food Color Induced Hepatotoxicity in Swiss Albino Rats, Rattus norvegicus. Toxicol Int 22, 152–157. Food Color Induced Hepatotoxicity in Swiss Albino Rats, Rattus norvegicus Toxicology International

SCF (Scientific Committee for Food), 1975. Reports from the Scientific Committee for Food (1st series), opinion expressed 27 June 1975. REPORTS OF THE SCIENTIFIC COMMITTEE FOR FOOD : First series

Shen, L., Ji, H.-F., 2012. The pharmacology of curcumin: is it the degradation products? Trends Mol Med 18, 138–144. https://doi.org/10.1016/j.molmed.2012.01.004

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., Srinivas, P.S., 1998. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 64, 353–356. https://doi.org/10.1055/s-2006-957450

Sterzi, S., Giordani, L., Morrone, M., Lena, E., Magrone, G., Scarpini, C., Milighetti, S., Pellicciari, L., Bravi, M., Panni, I., Ljoka, C., Bressi, F., Foti, C., 2016. The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study. Eur J Phys Rehabil Med 52, 321–330.

Stohs, S.J., Chen, O., Ray, S.D., Ji, J., Bucci, L.R., Preuss, H.G., 2020. Highly Bioavailable Forms of Curcumin and Promising Avenues for Curcumin-Based Research and Application: A Review. Molecules 25, 1397. https://doi.org/10.3390/molecules25061397

Suhail, F.K., Masood, U., Sharma, A., John, S., Dhamoon, A., 2020. Turmeric supplement induced hepatotoxicity: a rare complication of a poorly regulated substance. Clin Toxicol (Phila) 58, 216–217. https://doi.org/10.1080/15563650.2019.1632882

Thanawala, S., Shah, R., Doyle, L., Upadhyay, V., 2024. Comparative Pharmacokinetics of Curcuminoids from Water-Dispersible Turmeric Extract Against a Curcuminoids-Piperine Combination: An Open-Label, Randomized, Balanced, 2-Treatment, 2-Sequence, 2-Period Crossover Study. Altern Ther Health Med 30, 18–23. (abstract only).

Tsuda, S., Matsusaka, N., Madarame, H., Ueno, S., Susa, N., Ishida, K., Kawamura, N., Sekihashi, K., Sasaki, Y.F., 2000. The comet assay in eight mouse organs: results with 24 azo compounds. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 465, 11–26. https://doi.org/10.1016/S1383-5718(99)00199-0

Tullberg, S.C., Keene, W.E., Walton, K., Rakkar, P., Toor, M. and Renwick, A.G., 2004. Biomarkers, toxicokinetics and default uncertainty factors, Project Number – T01017 FSA. Studies on curcumin. pp 30-40. [ARCHIVED CONTENT] Food Standards Agency Report Repository::Search results page

Ullah, A., Chan, M.W.H., Aslam, S., Khan, A., Abbas, Q., Ali, Shamsher, Ali, M., Hussain, A., Mirani, Z.A., Sibt-e-Hassan, S., Kazmi, M.R., Ali, Shaukat, Hussain, S., Khan, A.M., 2022. Banned Sudan dyes in spices available at markets in Karachi, Pakistan. null 1–9. https://doi.org/10.1080/19393210.2022.2100489

Wahlström, B., Blennow, G., 1978. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol (Copenh) 43, 86–92. https://doi.org/10.1111/j.1600-0773.1978.tb02240.x

Wang, R., Han, J., Jiang, A., Huang, R., Fu, T., Wang, L., Zheng, Q., Li, W., Li, J., 2019. Involvement of metabolism-permeability in enhancing the oral

bioavailability of curcumin in excipient-free solid dispersions co-formed with piperine. International Journal of Pharmaceutics 561, 9–18. https://doi.org/10.1016/j.ijpharm.2019.02.027

WHO, 2022. Lead poisoning. Lead poisoning

Yang, K.-Y., Lin, L.-C., Tseng, T.-Y., Wang, S.-C., Tsai, T.-H., 2007. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 853, 183–189. https://doi.org/10.1016/j.jchromb.2007.03.010

Zhou, L., Zhang, K., Li, J., Cui, X., Wang, A., Huang, S., Zheng, S., Lu, Y., Chen, W., 2013. Inhibition of vascular endothelial growth factor-mediated angiogenesis involved in reproductive toxicity induced by sesquiterpenoids of Curcuma zedoaria in rats. Reprod Toxicol 37, 62–69. https://doi.org/10.1016/j.reprotox.2013.02.001

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

Annex A to the statement on the potential risk to human health of turmeric and curcumin supplements. Additional toxicological information

Introduction

1. The information presented in this Annex should be read in conjunction with the main draft statement on the potential risk to human health of turmeric and curcumin supplements. It contains further detailed information on curcuminoids in relation to toxicity covering both animal and human studies.

Curcuminoids and hepatotoxicity: Animal studies

Short-term studies of toxicity

Mice

2. Dietary turmeric powder (0%, 0.2%, 1.0%, 5.0%, equivalent to 0, 400, 2000, 10000 mg/kg bw/day) or ethanolic turmeric extract (ETE, 0%, 0.05 %, 0.25 %, equivalent to 0, 100, 500 mg/kg bw/day) for 14 days, at doses reported to be cancer preventive in model systems, were found to be hepatotoxic in mice. The curcumin contents of the turmeric powder and ETE were not reported. Exposure of mice to dietary turmeric or ETE did not have any significant effect on body weight/ liver weight or liver to body weight ratios. Animals exposed to 0.2 % turmeric showed coagulative necrosis in liver. Livers from mice receiving 1.0 % and 5.0 % turmeric showed extreme degenerative changes with necrosis. Coagulative necrotic foci surrounded by a zone of regeneration were also evident. Similar changes were also seen in animals treated with 0.05 % and 0.25 % ETE. Necrotic changes in liver, the

principal effect, was seen in 6/6 animals from 5.0 % turmeric, 3/6 from 1.0 % turmeric and 3/6 animals from 0.2 % turmeric. Similarly, 3/6 animals from 0.05 % as well as 0.25 % ETE also showed these alterations. Liver from mice receiving control diet showed normal ultrastructure. In the liver of the animals receiving 5.0 % or 1.0 % turmeric diet or 0.25 % or 0.05 % ETE, some of the parenchymal cells had round nuclei consisting of clumped or densely marginated chromatin. The cytoplasm consisted of numerous pleomorphic vacuolated mitochondria filled with dense bodies, surrounded by rough or smooth endoplasmic reticulum and free ribosomes, and an increased number of glycogen particles and Golgi complexes with vesicles (Kandarkar *et al*., 1998).

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

4. In a 13-week study, groups of 10 male and 10 female B6C3F1 mice were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin, which were estimated to deliver average daily doses of 0, 150, 750, 1700, 3850, or 7700 mg/kg bw to males and 0, 200, 1000, 1800, 4700 or 9300 mg/kg bw to females (NTP 1993). The major component of the oleoresin was identified as curcumin (79 to 85 %). The percent composition was monitored periodically at the study laboratory with free-acid titration and high-performance liquid chromatography methods, and no change in composition was observed. There were no deaths attributed to turmeric oleoresin and the final mean body weight gains and final mean body weights

of all exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that by the controls. Absolute and relative liver weights of male mice that received 5000 ppm and male and female mice that received 10000, 25000 and 50000 ppm were significantly greater than those of the controls. These changes were not considered adverse. Clinical findings in mice included stained fur, and discoloured faeces and urine. According to NTP, there were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters, and there were no chemical related histopathologic lesions. JECFA concluded that the no observed adverse effect level (NOAEL) in mice was 7700 and 9280 mg/kg bw/day in males and females, respectively, which were the highest doses tested (cited in EFSA, 2010). The EFSA ANS Panel (2010) agreed with the NOAEL concluded by JECFA.

Rats

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

6. In a 28-day study, curcumin (purity > 98 %) was administered to male Sprague Dawley rats through the diet at dose levels of 0, 26.1, 84.8, 224,8, 459.7 and 1117.8 mg/kg bw/day. Clinical chemistry did not reveal major signs of liver damage associated with administration of the compound. cDNA microarray experiments were performed on hepatic RNA. Curcumin altered

the expression of 12 genes. Three of these were related to peroxisomes (phytanoyl-CoA dioxygenase, enoyl-CoA hydratase; CYP4A3). Increased cyanide insensitive palmitoyl-CoA oxidation was observed. The authors concluded that these data suggest that curcumin is a weak peroxisome proliferator in rats (Stierum *et al*., 2008).

7. In a 13-week study, groups of 10 male and 10 female F344/N rats were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin (79 to 85 % curcumin), estimated to deliver average daily doses of 0, 50, 250, 480, 1300, or 2600 mg/kg bw to males and 0, 60, 300, 550, 1450, or 2800 mg/kg bw to females. All rats survived until the end of the study. The final mean body weight of males receiving 50000 ppm was 5 % lower than that of the controls. Feed consumption by exposed male and female rats was similar to that of controls. The absolute and relative liver weights of female rats and the relative liver weights of male rats receiving ≥ 5000 ppm were significantly greater than those of the controls. According to the NTP, these increases may have been due to mild hepatocellular swelling or hypertrophy. In the clinical chemistry, urinalysis, and hematologic assessment, no differences were observed that were considered by the NTP to be biologically significant. Clinical findings included stained fur, and discoloured faeces and urine of exposed animals. Mild to moderate hyperplasia of the mucosal epithelium was observed in the cecum and colon of male and female rats that received 50000 ppm. The authors did not attempt to identify a NOAEL, as this was a dose range-finding study (NTP 1993).

8. A six-month toxicity study of curcuminoids extracted from the powdered dried rhizome of *Curcuma longa* was performed in six groups of 15 Wistar rats of each sex. The extract was reported to contain 58-67 % curcuminoids. The water control group received 5 ml of water/kg bw/day, while the tragacanth (plant-derived gum) control group received 5 ml of 0.5 % tragacanth suspension/ kg bw/day orally. Three treatment groups were given the suspension of curcuminoids powder at doses of 10, 50 and 250 mg/kg bw/day. The fourth treatment group, or the recovery group, also received 250 mg/kg bw/day of curcuminoids for six months, but two weeks of no

curcuminoids treatment elapsed before the time of termination. The exact method of administration was not described. The growth rate of male rats receiving curcuminoids at 50 mg/kg bw/day was significantly higher than that of the tragacanth control group. Curcuminoids did not produce any significant dose-related changes of haematological parameters. In male animals receiving 250 mg/kg bw/day of curcuminoids, actual and relative liver weights and the level of serum alkaline phosphatase (ALP) were significantly higher than those of the two controls, but the ALP level was still within a normal range. There appeared to be a higher incidence of mild degree of liver fatty degeneration and adrenocortical fatty degeneration in this group of animals, however the incidence was not significantly different from that of the two controls. The authors concluded that at higher doses, curcumin may affect the function and morphology of the liver in a reversible manner. The EFSA ANS Panel (2010) concluded that due to the lack of knowledge on the curcumin content and nature of the extract tested, the study could not be used to assess the safety of curcumin (Chavalittumrong *et al.*, 2002).

9. Majeed *et al*., (2023) performed a battery of toxicological studies with “AC 3®”, a BDMC enriched *C. longa* extract, obtained through solvent extraction, standardized to contain a minimum of 85% w/w of total curcuminoids by HPLC and with BDMC in the range of 30 – 35%.

10. An acute toxicity study at a gavage dose of up to 2000 mg/kg bw (i.e., maximum recommended by the test guidelines) did not result in any clinical signs of toxicity in female adult Wistar rats. A subacute 28-day oral toxicity study in males and females was undertaken with low, mid, and high gavage doses of 125, 250, and 500 mg/kg/bw per day. No changes were observed in body weight gain and feed consumption. No treatment-related changes were observed in haematological, biochemical, or urine parameters, nor in organ weights and gross and histopathological examination. A sub chronic oral toxicity study was performed in male and female Wistar rats at gavage doses 125, 250, and 500 mg/kg bw/day for 90 days. The authors state that “administration [of the test substance] showed no mortality and clinical signs of toxicity. No significant difference was observed in feed consumption, body

weight, as well as percentage body weight change. Similarly, there were no significant changes in neurological, ophthalmological, haematological, and biochemical parameters as well as urine analysis. The necropsy did not reveal any treatment-related pathological significance. There were no treatment-related changes observed in absolute and relative organ weights. Majeed *et al*., (2023)"

11. Nirvanashetty *et al*., (2022) conducted a series of safety studies on a proprietary oleoresin-based turmeric extract (CURCUGEN®). These studies were designed as a preclinical safety assessment. The test substance was referred to by the authors as "a standardized curcuminoid extract with 50% curcuminoid, 1.5% essential oils, and other constituents of turmeric." In a repeat dose 90-day oral toxicity test the extract was administered to male and female Sprague-Dawley rats at a gavage dose level of 2000 mg/kg bw/day. This study omitted a low and mid dose because, based on their interpretation of the OECD guidelines, the authors argued that "The limit test precludes the need for full study of three dose levels." The authors reported that "There was no treatment-related variation in the mean body weight or percent body weight change with respect to day 1 in the limit dose of 2000 mg/kg/day. No treatment-related changes in feed consumption were noted in both the main group and recovery group animals." Moreover, there were no opthalmological abnormalities, no treatment-related effects on neurological examination, and "no adverse treatment-related changes in haematology parameters were noted." There were some changes in haematological parameters that the authors considered to not be test item related." There were no treatment-related adverse effects in the other parameters measured, including blood biochemistry, gross necropsy, and histopathology. Overall, the authors concluded that based on the observed results in rats receiving the test item at 2000 mg/kg bw/day by gavage (orally) over 90 consecutive days, a no observed adverse effect level (NOAEL) of 2000 mg/kg bw/day was identified.

Chronic toxicity

Two years study in mice

12. Groups of 60 male and 60 female B6C3F1 mice were fed diets containing 0, 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % curcumin) for 103 weeks, which were estimated to deliver average daily doses of 0, 220, 520, or 6000 mg/kg bw per day to males and 0, 320, 1620, or 8400 mg/kg bw per day to females (NTP 1993). Nine or ten mice from each exposure group were evaluated after 15 months. Survival of exposed male and female mice was similar to that of the controls. The mean body weight of female mice receiving 50000 ppm was slightly lower (up to 12 %) than that of the controls from about week 25. The final mean body weights of males that received 50000 ppm and females that received 10000 and 50000 ppm were significantly lower than those of controls. The final mean body weights of other exposed groups of male and female mice were similar to those of the controls. Feed consumption by exposed male and female mice was similar to that of the controls throughout the study. The absolute and relative liver weights of male and female mice receiving 10000 and 50000 ppm were significantly greater than those of the controls at the 15-month interim evaluation. There were no clinical findings related to toxicity. No biologically significant differences were observed in hematologic parameters. The alkaline phosphatase (ALP) values of male and female mice that received 10000 and 50000 ppm were significantly higher than those of controls at the 15-month interim evaluation. The incidence of thyroid gland follicular cell hyperplasia was statistically significantly increased in high dose female mice. The incidences of hepatocellular adenoma in male and female mice receiving 10000 ppm (the mid dose group), but not those in mice receiving 2000 or 50000 ppm, were significantly increased (male: 25/50, 28/50, 35/50, 30/50; female: 7/50, 8/50, 19/51, 14/50). The number of male and female mice in the 10000 and 50000 ppm groups with multiple hepatocellular neoplasms compared with controls was statistically significantly increased. However, JECFA concluded that these effects were not dose-related and that curcumin is not a carcinogen in mice (FAO/WHO 1995). In addition, the EFSA ANS Panel (2010) noted that all statistically significant effects noted by the NTP refer to benign neoplastic lesions (adenomas). The EFSA Panel noted that

the effects observed were not dose-dependent, were in line with historical control values and were not consistent across sexes and/or species. The Panel noted moreover that “hepatocellular tumours occurring in untreated and treated B6C3F1 mice are not relevant for humans”.

Two years study in rats

13. Groups of 60 male and 60 female F344/N rats were fed diets containing 0, 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % curcumin) for 104 (males) or 103 (females) weeks, which were estimated to deliver average daily doses of 0, 80, 460, or 2000 mg/kg bw per day to males and 0, 90, 440, or 2400 mg/kg bw per day to females. Nine or 10 rats from each exposure group were evaluated after 15 months. Survival of exposed male and female rats was similar to that of the controls. The final mean body weights of all exposed male rats and female rats receiving 2000 and 10000 ppm were similar to those of the controls. The final mean body weights of male and female rats that received 50000 ppm were slightly lower (up to 10 %) than those of the controls throughout much of the study. Feed consumption by exposed male and female rats was similar to that of controls throughout the study. The absolute and relative liver weights of female rats receiving 10000 or 50000 ppm were significantly greater than those of controls at the 15-month interim evaluation. There were no clinical findings related to toxicity. In male and female rats receiving 50000 ppm the haematocrit values, haemoglobin concentrations and erythrocyte counts at the 15-month interim evaluation were significantly lower than those in the controls. In addition, platelet counts in male and female rats that received 50000 ppm and reticulocyte counts in male rats that received 50000 ppm were significantly higher than those in the controls. No biologically significant differences were observed in clinical chemistry parameters. Gastrointestinal irritation (ulcers, hyperplasia and inflammation) was observed in high dose males and females. The incidence of clitoral gland adenomas (females) was statistically significantly increased in treated animals (NTP, 1993), JECFA concluded that these effects were not dose-related and that curcumin was not a carcinogen in rats. The authors did not attempt to identify a NOAEL for this

study (NTP 1993), but JECFA identified a NOAEL for the gastrointestinal effects of 440 mg/kg bw/day.The EFSA Panel noted that all statistically significant tumourigenic effects observed in the NTP studies in rats and mice related to benign lesions (adenomas) and that the incidences for carcinomas did not reach statistical significance. The Panel also noted that the effects observed were not dose-dependent, were in line with historical control values and were not consistent across sex and/or species. The Panel also noted that the hepatocellular tumours observed in B6C3F1 mice are not relevant for humans. Therefore, the Panel agreed with the overall conclusion of JECFA that curcumin is not carcinogenic.

Human Studies

14. Twenty-five patients with conditions indicating a high risk of malignancy were administered diferuloylmethane (curcumin) (purity 99.3 %) in tablet form for 3 months. The starting dose was 500 mg/day, which was increased stepwise to 1000, 2000, 4000, 8000 and finally 12000 mg/day (equivalent to 7, 14, 29, 57, 114, and 171 mg/kg bw/day). The patients received regular follow-up, including physical examination, weekly haemogram, and “biweekly” blood electrolytes and biochemistry study (though blood results not presented). No adverse effects were reported at doses up to 8000 mg/day. The highest dose of 12000 mg/day was not acceptable to the patients because of the bulky volume of the tablets. The serum concentration of curcumin usually peaked at 1 to 2 hours after oral intake of diferuloylmethane and gradually declined within 12 hours. The average peak serum concentrations after taking 4000 mg, 6000 mg and 8000 mg of curcumin were 0.51 ± 0.11 μM, 0.63 ± 0.06 μM, and 1.77 ± 1.87 μM, respectively. Urinary excretion of diferuloylmethane was undetectable. The study authors noted that these results suggest that diferuloylmethane is not adequately absorbed from the gastrointestinal tract. (Cheng *et al*., 2001).

15. In a dose escalation study fifteen patients with advanced colorectal cancer received an extract of Curcuma (containing 20 mg of curcuminoids, 18 mg of diferuloylmethane and 2 mg of demethoxycurcumin suspended in 200

mg of essential oils derived from *Curcuma spp*.) daily for up to 4 months. Doses were equivalent to 36, 72, 108, 144 and 180 mg diferuloylmethane/day. There were three patients per dose. Neither diferuloylmethane, nor its metabolites (glucuronide or sulfate conjugates, hexahydrocurcumin or hexahydrocurcuminol) were detected in plasma or urine over up to 29 days of daily treatment. However, diferuloylmethane was detected in the faeces of all patients. Diferuloylmethane sulfate was also detected in the faeces of one of the patients receiving diferuloylmethane at a dose of 180 mg/day, which may have been a result of biotransformation in the gut. The study authors therefore concluded that diferuloylmethane has low oral bioavailability in humans and may undergo intestinal metabolism. Oral Curcuma extract was well tolerated, and no dose-limiting toxicity was observed. However, gastrointestinal effects were reported, with one patient (receiving 108 mg diferuloylmethane/day) experiencing nausea and two patients (receiving 72 and 180 mg diferuloylmethane /day) experiencing diarrhoea. (Sharma *et al*., 2001).

16. In a subsequent phase I study, Sharma *et al.,* (2004) evaluated another formulation, which was a 500 mg curcuminoid capsule containing 450 mg diferuloylmethane, 40 mg demethoxycurcumin, and 10 mg bisdemethoxycurcumin. The dose levels of diferuloylmethane were 450, 900, 1800, or 3600 mg/day for up to 4 months (equivalent to 6, 13, 26, and 51 mg/kg bw/day). A total of 15 patients with refractory colorectal cancer were enrolled. Full blood cell count and urea, electrolytes, liver and bone function were measured in venous samples, and physical examination was performed, before treatment and on treatment days 1, 2, 8, 29, and monthly thereafter. The drug was well tolerated and dose-limiting toxicity was not observed. However, one patient consuming 450 mg diferuloylmethane daily and one patient consuming 3600 mg diferuloylmethane daily developed diarrhoea 1 month and 4 months into treatment, respectively. One patient consuming 900 mg diferuloylmethane daily experienced nausea, which resolved spontaneously despite continuation of treatment. In addition, a rise in serum alkaline phosphatase (ALP) level was observed in 4 patients, and serum lactate dehydrogenase (LDH) rose to > 150 % of pre-treatment values in 3

patients. Diferuloylmethane was detected in the plasma (at 1-hour post dosing) from three out of the six patients consuming 3600 mg of diferuloylmethane daily, but not from patients receiving the lower doses. The mean plasma concentration of diferuloylmethane in these three patients was 11.1 ± 0.6 nmol/L. Moreover, glucuronides and sulfates of diferuloylmethane and desmethoxycurcumin were found in the plasma from all 6 of the patients consuming 3600 mg of curcumin daily at all the time points studied. Analysis of urine suggested the presence of diferuloylmethane (0.1 - 1.3 µmol/L) and its sulfate (19 - 45 nmol/L) and glucuronide (210 - 510 nmol/L) conjugates in all of the samples from patients consuming 3600 mg of diferuloylmethane daily. Diferuloylmethane was not detected in plasma or urine from patients who received lower doses of diferuloylmethane. Abundant amounts of diferuloylmethane were recovered from the faeces at all of the dose levels. Diferuloylmethane levels in day 8 faecal samples from patients consuming 3600 mg of diferuloylmethane daily were between 25 and 116 nmol/g dried faeces.

17. A dose escalation study was performed with 24 healthy human volunteers using single doses of between 500-12000 mg of a turmeric extract (containing a minimum of 95 % of diferuloylmethane (75 %), bisdemethoxycurcumin (2 %), and demethoxycurcumin (23 %), equivalent to 7-171 mg/kg bw). Seven volunteers experienced minimal toxicity at doses > 14 mg/kg bw (diarrhoea, headache, rash and/or yellow stool) that did not appear to be dose-related. The remaining volunteers did not experience adverse effects (Lao *et al.,* 2006).

18. Nine healthy volunteers between 20 and 33 years of age were tested for haemoglobin, blood counts, liver and kidney functions, bleeding and clotting time and serum electrolytes initially and at 1 and 3 months of treatment. They were administered 0.6 ml of turmeric oil extract (TO; 59 % turmerone and Ar-turmerone) three times a day for 1 month and 1 ml in 3 divided doses for 2 months. One volunteer discontinued on day three because of allergic skin rashes which, on discontinuation of TO, gradually disappeared by two weeks. Another discontinued on day seven for intercurrent fever

requiring antibiotic treatment. Seven volunteers completed the study. There was no effect of TO intake on bodyweight, blood pressure, symptoms and signs up to 12 weeks. There was no clinical, haematological, renal or hepatotoxicity of TO at 1 month and 3 months. Serum levels of AST, ALT, ALP, albumin, direct and indirect bilirubin were normal initially and remained within normal limits during treatment. One volunteer showed normal serum triglycerides and low-density lipoprotein (LDL) initially and at 4 weeks but elevated levels at 12 weeks. This volunteer was followed up for 1 month after discontinuation of TO and serum lipids returned to normal. (Joshi *et al.,* 2003).

19. Kanai *et al.,* (2011) evaluated the safety and feasibility of combination therapy using “curcumin” with gemcitabine-based chemotherapy. The ”curcumin” used was a mixture of diferuloylmethane (73 %), demethoxycurcumin (22 %), and bisdemethoxycurcumin (4 %), provided in microbead form. Gemcitabine-resistant patients with pancreatic cancer received 8 g oral curcumin daily (equivalent to 114 mg/kg bw) in combination with gemcitabine-based chemotherapy. The primary endpoint was safety for phase I and feasibility of oral curcumin for phase II study. Twenty-one patients were enrolled. No dose-limiting toxicities were observed in the phase I study and oral curcumin 8 g/day was selected as the recommended dose for 17 patients in the phase II study. No patients were withdrawn from this study because of the intolerability of curcumin, which met the primary endpoint of the phase II study, and the median compliance rate of oral curcumin was 100 % (range 79-100 %). Plasma curcumin levels ranged from 29 to 412 ng/ml in five patients tested. Adverse effects were reported (neutropenia, fatigue, drowsiness, anorexia, obstruction of the gastrointestinal tract, and oedema) all of which were also attributed to disease progression or gemcitabine-based chemotherapy, and considered to be irrelevant to curcumin. Kanai *et al*. (2011) concluded that combination therapy using 8 g oral curcumin daily with gemcitabine-based chemotherapy was safe and feasible in patients with pancreatic cancer and warrants further investigation into its efficacy.

20. In September 2018, the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) considered several clinical

studies with turmeric preparations involving patients with digestive disorders. Although a possible effect in improving symptoms was seen, firm conclusions could not be drawn due to limitations in the study design, for example only one study compared turmeric with a control group. However, the HMPC considered the effectiveness of these preparations for relief of mild digestive problems to be plausible and there is evidence that they have been used safely in this way for at least 30 years (including at least 15 years within the European Union). Thus, the HMPC concluded that turmeric preparations (which cover turmeric ground powders and extracts) can be used (only by adults) for relief of mild problems with digestion, such as feelings of fullness, slow digestion and flatulence. This conclusion was based on long-standing use and not on clear evidence of efficacy. The EMA considered that side effects of dry mouth, flatulence and stomach irritation may occur. If symptoms continue for longer than two weeks or worsen while taking the medicine, a qualified healthcare practitioner should be consulted.

Curcuminoids and hepatotoxicity: Case studies in humans

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

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

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

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

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

26. A 55-year-old man was found to have an asymptomatic transaminitis at a routine check-up. His background history included idiopathic thrombocytopenic purpura, hypertension, gout, and osteoarthritis, with regular medications including long-term telmisartan, atenolol, and lercanidipine. He had no known liver history, with normal liver function tests one year prior. His

only new medication was commencement of a turmeric supplement five months prior to testing. He was referred to a hepatologist and underwent a screen for causes of acute hepatitis. Abdominal ultrasonography showed diffuse steatosis. A drug reaction was suspected, and the turmeric supplement was ceased. Follow-ups occurred over the subsequent four months. Near normalisation of liver function tests occurred by one month (ALT 96 U/L, bilirubin 10 μmol/L) with further improvement by four months after cessation (ALT 46 U/L, bilirubin 11 μmol/L). The turmeric supplement was the presumed cause of the hepatitis. The turmeric supplement was not identified, thus further analysis on it could not be performed and hence dose information is unknown. (Luber *et al. 2019)*.

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

28. Suhail *et al*. (2020) noted that the temporal association of liver injury in the patient, normalisation of LFTs upon withdrawal and improvement with steroids implicate the turmeric supplement as the likely causative agent of liver injury. The Roussel-Uclaf Causality Assessment Method (RUCAM) scale, which attempts to codify causality of drug toxicity into objective criteria, was eight in the patient indicating a probable adverse drug reaction. A negative serological workup and normalisation of LFTs following the discontinuation of steroids further solidify this conclusion.

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

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

curcuminoids derived from the turmeric supplement that the patient was still consuming at the time of the biopsy.

31. Smati *et al*., (2023) report a case report of turmeric-induced liver injury in a 36-year-old woman with minimal alcohol use and no use of prescription or over-the-counter medications, acetaminophen, tobacco, or recreational drugs who had been taking approximately 2g turmeric per day. The patient showed increased liver enzymes and bilirubin. Liver biopsy was notable for chronic portal triaditis, bile ductular injury, and patchy hepatocellular necrosis consistent with hepatocellular liver injury. Her liver functions showed gradual but steady improvement. Post-discharge, liver tests (aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > alkaline phosphatase (ALP)) slowly decreased to relatively normal values 31 days after stopping turmeric intake. By the point that she presented as an outpatient for her 6-month post-discharge follow-up, her liver function test results were all normal. The discussion of the article suggests that “Despite significant underreporting of HDS [herbal and dietary supplements]-associated adverse events, approximately 20% of documented drug-induced liver injuries are secondary to HDS.” Through reference to the wider literature, the authors go on to argue that there is a “a dose-dependent relationship between curcumin absorption and liver injury” and that “further complicating safe dosage of [curcumin] are factors such as form of delivery and inclusion of bioavailability-increasing substances like piperine.”

32. A case study of potential drug-induced liver injury related to turmeric consumption was reported by Ajitkumar *et al*., 2023. The patient was a 55-year-old woman with progressive jaundice and elevated bilirubin and liver enzymes but without evidence of acute liver failure. The patient had been taking 2g turmeric once daily for wrist pain for approximately one month prior to presentation. Her liver function tests normalized 2 months after her initial presentation and cessation of turmeric supplement intake.

List of Abbreviations and Technical terms

ADI	Acceptable Daily Intake
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
AST	Aspartate Aminotransferase
cDNA	complementary Deoxyribonucleic acid
CYP	P450
dL	Decilitre (100 millilitres)
EFSA EMA	European Food Safety Authority European Medicines Agency
ETE	Ethanolic Turmeric Extract
FAO	Food and Agricultural Organisations of the United Nations
g	gram
GGT	Gamma-Glutamyl Transferase
HDS	Herbal and Dietary Supplements
HMPC	Committee on Herbal Medicinal Products
IgG	Immunoglobulin G
JECFA	Joint FAO-WHO Expert Committee on Food Additives
kg bw/day	Kilogram Bodyweight per Day
L	Litre
LDL	Low-Density Lipoprotein
LFTs	Liver Function Tests
mg	Milligram
mg/kg bw/day ml	Milligrams per Kilogram Bodyweight per Day Millilitre
ng	Nanogram
nMol	Nanomole
NOAEL	No-Observed-Adverse-Effect Level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development

ppm	Parts per million
RNA	Ribonucleic acid
RUCAM	Roussel-Uclaf Causality Assessment Method
SBB	Sudan Black B
TEO	Turmeric Essential Oil
TO	Turmeric Oil extract
U	Enzyme unit
µg	Microgram
µM / µMol	Micromole
WHO	World Health Organisation

References

Ajitkumar, A., Mohan, G., Ghose, M., Yarrarapu, S. and Afiniwala, S. 2023. Drug-Induced Liver Injury Secondary to Turmeric Use. Eur J Case Rep Intern Med 10, 003845. https://doi.org/10.12890/2023_003845

Chavalittumrong, P., Chivapat, S., Rattanajarasroj, S., Punyamong, S., Chuthaputti, A., Phisalaphong, C., 2002. Chronic toxicity study of curcuminoids in rats. Songklanakarin J. Sci. Technol. 24, 16.

Cheng, A.L., Hsu, C.H., Lin, J.K., *et al*. 2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Research 21**:** 2895-2900.

Deshpande, S.S., Lalitha, V.S., Ingle, A.D., Raste, A.S., Gadre, S.G., Maru, G.B., 1998. Subchronic oral toxicity of turmeric and ethanolic turmeric extract in female mice and rats. Toxicol. Lett. 95, 183–193. https://doi.org/10.1016/s0378-4274(98)00035-6

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010. Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive. EFSA J. 8. https://doi.org/10.2903/j.efsa.2010.1679

EMA (European Medicines Agency) (2018) Committee on Herbal Medicinal Products (HMPC) Assessment report on Curcuma longa L., rhizome. Turmeric

FAO/WHO, 1995. Evaluation of certain food additives and naturally occurring toxicants (Fourty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives).WHO Technical Report Series, No. 859. WHO_TRS_859.pdf

Joshi, J., Ghaisas, S., Vaidya, A., Vaidya, R., Kamat, D.V., Bhagwat, A.N. and Bhide, S. 2003. Early human safety study of turmeric oil (Curcuma longa oil)

administered orally in healthy volunteers. Journal of Association of Physicians of India 51: 1055-60.

Kanai, M., Yoshimura, K., Asada, M. et al. 2011. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer Chemother Pharmacol 68: 157-164 https://doi.org/10.1007/s00280-010-1470-2

Kandarkar, S.V., Sawant, S.S., Ingle, A.D., Deshpande, S.S., Maru, G.B., 1998. Subchronic oral hepatotoxicity of turmeric in mice-histopathological and ultrastructural studies. Indian J. Exp. Biol. 36, 675–679.

Lao, C.D., Ruffin, M.T., Normolle, D., *et al*. 2006. Dose escalation of a curcuminoid formulation. Complementary and Alternative Medicine 6: 10. https://doi.org/10.1186/1472-6882-6-10

Liju, V.B., Jeena, K., Kuttan, R., 2013. Acute and subchronic toxicity as well as mutagenic evaluation of essential oil from turmeric (Curcuma longa L). Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc. 53, 52–61. https://doi.org/10.1016/j.fct.2012.11.027

Lukefahr, A.L., McEvoy, S., Alfafara, C., Funk, J.L., 2018. Drug-induced autoimmune hepatitis associated with turmeric dietary supplement use. BMJ Case Rep. bcr-2018-224611. https://doi.org/10.1136/bcr-2018-224611

Luber, R.P., Rentsch, C., Lontos, S., Pope, J.D., Aung, A.K., Schneider, H.G., Kemp, W., Roberts, S.K., Majeed, A., 2019. Turmeric Induced Liver Injury: A Report of Two Cases. Case Reports Hepatol 2019, 6741213. https://doi.org/10.1155/2019/6741213

Majeed, M., Bani, S., Pandey, A., Ibrahim A, M., & Thazhathidath, S. (2023). Assessment of safety profile of activated curcumin C3 complex (AC3®), enriched extract of bisdemethoxycurcumin from the rhizomes of Curcuma longa. Journal of Toxicology, 2023(1), 3729399.

https://doi.org/10.1155/2023/3729399

National Toxicology Program (NTP), 1993. Toxicology and Carcinogenesis Studies of Turmeric Oleoresin (Cas No. 8024-37-1) (Major Component 79%-85% Curcumin, Cas No. 458-37-7) in F344/N Rats and B6C3F1 Mice (Feed Studies). Technical Report Series No. 427, NIH Publication No. 93-3158. U.S. TR-427: Turmeric Oleoresin (CASRN 8024-37-1) (Major Component 79% Curcumin, CASRN 458-37-7) in F344/N Rats and B6C3F1Mice (Feed Studies).

Nirvanashetty, S., Panda, S. K., & Jackson-Michel, S. (2022). Safety Evaluation of Oleoresin-Based Turmeric Formulation: Assessment of Genotoxicity and Acute and Subchronic Oral Toxicity. BioMed Research International, 2022(1), 5281660. https://doi.org/10.1155/2022/5281660

Smati, N., Xue, C., Vallabhaneni, M., Oduyebo, I., 2023. A Case of Turmeric-Induced Liver Injury. Annals of Internal Medicine Clinical Cases. https://doi.org/10.7326/aimcc.2023.0090

Sharma, R.A., McLelland, H.R., Hill, K.A., *et al*. 2001. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clinical Cancer Research 7**:** 1894-1900.

Sharma, R.A., Euden, S.A., Platton, S.L., *et al*. 2004. Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. Clin Cancer Res 10**:** 6847-6854. https://doi.org/10.1158/1078-0432.ccr-04-0744

Stierum, R., Conesa, A., Heijne, W., Ommen, B. van, Junker, K., Scott, M.P., Price, R.J., Meredith, C., Lake, B.G., Groten, J., 2008. Transcriptome analysis provides new insights into liver changes induced in the rat upon dietary administration of the food additives butylated hydroxytoluene, curcumin, propyl gallate and thiabendazole. Food Chem. Toxicol. 46, 2616–2628. https://doi.org/10.1016/j.fct.2008.04.019

Suhail, F.K., Masood, U., Sharma, A., John, S., Dhamoon, A., 2020. Turmeric supplement induced hepatotoxicity: a rare complication of a poorly regulated substance. Clin. Toxicol. Phila. Pa 58, 216–217. https://doi.org/10.1080/15563650.2019.1632882

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

Annex B to the statement on the potential risk to human health of turmeric and curcumin supplements. Additional exposure and analytical data

Introduction

1. The information presented in this Annex should be read in conjunction with the main draft statement on the potential risk to human health of turmeric and curcumin supplements. It contains further detailed information on exposure data for turmeric in food and the presentation of trace element contamination from a recent survey.

Exposure from curcuminoids in food

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

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

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

3. The EFSA ANS panel (2010) estimated dietary exposure to curcumin in children and adults using national consumption data with maximum permitted levels (MPLs) specified in Directive 94/36/EC (EC 1994) (tier 2 approach), and maximum reported use levels (tier 3 approach). Estimates of dietary exposure to curcumin obtained from these approaches are presented in Table 2.

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

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

Maximum permitted level (tier 2):	**UK adult exposure (> 18 years old) to curcumin (mg/kg bw/day)**	**Children (UK, 1.5 – 4.5 years & EXPOCHI, 1-10 years old) exposure to curcumin (mg/kg bw/day)**
Mean exposure	0.9	0.5-3.8
Exposure 95th or 97.5th %ile †	3.3	1.2-7.2
Maximum reported use levels (tier 3):	**UK adult exposure (> 18 years old) to curcumin (mg/kg bw/day)**	**Children (UK, 1.5 – 4.5 years & EXPOCHI, 1-10 years old) exposure to curcumin (mg/kg bw/day)**
Mean exposure	0.8 (1.0 *)	0.5-3.4 (0.7-3.6 *)
Exposure 95th or 97.5th %ile †	2.0 (2.6 *)	1.1-7.1 (1.6-7.6 *)

* Includes dietary exposure to curcumin from turmeric powder added to food as a spice and curry powder (see Table 3).
† For UK children and adults, mean consumption plus intake at the 97.5th percentile of 'spirituous beverages'). For EU children, estimates are based on the EXPOCHI report, which gives the 95th percentile intake.

5. In tier 2, the main contributor to curcumin exposure from the UK adult diet was non-alcoholic flavoured drinks (46 %). The main contributors to the estimates of mean curcumin exposure for UK children, between 1.5 and 4.5 years old, (and children between 1 and 10 years old considered by the EXPOCHI consortium) were non-alcoholic beverages (13-55 %), fine bakery wares (e.g., biscuits, cakes, wafer) (12-43 %), desserts, including flavoured milk products (12-45 %), and sauces, seasonings, pickles, relishes, chutney and piccalilli (11-42 %).

6. In tier 3, the main contributor to curcumin exposure from the UK adult diet was non-alcoholic flavoured drinks (50 %). The main contributors to the estimates of mean curcumin exposure for UK children, between 1.5 and 4.5 years old, (and children between 1 and 10 years old considered by the EXPOCHI consortium) were fine bakery wares (e.g., biscuits, cakes, wafer) (13-47 %), desserts (including flavoured milk products) (13-52 %), non-alcoholic beverages (15-57 %) and sauces and seasonings (11-45 %).

7. The exposure assessment in tier 3 does not take into account the use of turmeric as a spice in cooking. The estimated additional dietary exposure to curcumin through the use of turmeric spice in cooking was calculated by the EFSA ANS panel (2010) and is displayed in Table 3.

8. Because of the estimated exceedances of the ADI by 1 – 10-year-olds in the 2010 assessment, EFSA undertook a refined assessment of exposure to curcumin in the EU diet (EFSA, 2014). The refined assessment utilised consumption data from the Comprehensive European Food Consumption Database which contains data from EU Member States at the time of the assessment. Each age category was contributed to by a range of countries

and consumption by the UK population was represented only in the “adult” category (18 – 60-years-old). The refined assessment also used additional data on curcumin levels reported to EFSA between 2010 and 2014.

9. Using this data, the 2014 assessment estimated exposure to curcumin under three different scenarios: Using maximum permitted levels; using reported use levels based on a “brand-loyal” scenario; and using reported use levels based on a “non-brand-loyal" scenario. The estimated exposures are displayed in table 4.

10. For children (no UK estimates), adolescents (no UK estimates), adults (UK estimates included), and the elderly (no UK estimates), the main food categories contributing to curcumin exposure in the 2014 assessment were flavoured drinks and fine bakery wares. For toddlers (no UK estimates), the main contributing food categories were flavoured fermented milk products and fine bakery wares. These food categories were the main contributors regardless of the exposure assessment scenario.

11. Overall, the curcumin exposures estimated in EFSA’s 2014 assessment were lower than those estimated in 2010. Whilst UK NDNS data for adult consumption of curcumin was included in the 2014 estimate as one of 15 consumption surveys, the UK data was the only survey considered in the 2010 estimate for adult exposures.

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

Exposure from spice added to food *	**Adult (18-64 years old) curcumin exposure (mg/kg bw/day)**	**Children (5-12 years old) curcumin exposure (mg/kg bw/day)**
Mean	0.1 (n = 66)	0.1 (n = 7)
97.5th %ile	0.3 (n = 66)	0.2 (n = 7)
Exposure from curry powder added to food *	**Adult (18-64 years old) curcumin exposure (mg/kg bw/day)**	**Children (5-12 years old) curcumin exposure (mg/kg bw/day)**
Mean	0.1 (n = 91)	0.1 (n = 21)
97.5th %ile	0.3 (n = 91)	0.3 (n = 21)

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

Table 4. Estimated exposures to curcumin in the EU population (from EFSA, 2014).

Maximum permitted levels	Toddlers (12 – 35 months) (mg/kg bw/day)	Children (3 – 9 years) (mg/kg bw/day)	Adolescents (10 – 17 years) (mg/kg bw/day)	Adults (18 – 64 years) (mg/kg bw/day)	The elderly (>65 years) (mg/kg bw/day)
Mean	0.9-3.9	0.9-3.2	0.3-1.6	0.3-1.1	0.1-0.6
High level	2.8-7.2	2.0-6.7	1.0-3.3	0.7-2.3	0.5-1.4
Refined scenario	n/a	n/a	n/a	n/a	n/a
Brand-loyal	n/a	n/a	n/a	n/a	n/a
Mean	0.4-2.0	0.6-1.6	0.2-0.9	0.2-0.6	0.1-0.4
High level	1.4-3.3	1.2-3.4	0.7-2.3	0.4-1.5	0.3-0.9
Non-brand-loyal	n/a	n/a	n/a	n/a	n/a
Mean	0.1-0.8	0.2-0.6	0.1-0.3	0.1-0.2	0.03-0.2
High level	0.5-1.2	0.5-1.2	0.2-0.7	0.2-0.5	0.1-0.4

Contamination of raw, ground turmeric and curcumin supplements

Heavy metals

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

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

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

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

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

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

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

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

TUI = Tolerable Upper Intake.

TDI = Tolerable Daily Intake.

p-RFD = Provisional Reference Dose.

ADI = Acceptable Daily Intake.

n/a = not applicable.

List of Abbreviations and Technical terms

ADI	Acceptable Daily Intake
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources Added to Food
As	Arsenic
Cd	Cadmium
EFSA	European Food Safety Authority
EU	European Union
EXPOCHI	Exposure Assessments For Children In Europe
g	gram
HBGVs	Health-Based Guidance Values
Hg	Mercury
kg bw/day	Kilogram Bodyweight per Day
mg	Milligram
MPL	Maximum Permitted Levels
NDNS	National Diet and Nutrition Survey
p-RFD	Provisional Reference Dose
Pb	Lead
SD	Standard Deviation
TDI	Tolerable Daily Intake
TUI	Tolerable Upper Intake
µg	Microgram
UK	United Kingdom

References

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), 2010. Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive. EFSA J. 8. https://doi.org/10.2903/j.efsa.2010.1679

EFSA, 2014. Refined exposure assessment for curcumin (E 100). EFSA Journal, 12:10, 3876. https://doi.org/10.2903/j.efsa.2014.3876

Harrington, K.E., Robson, P.J., Kiely, M., Livingstone, M.B., Lambe, J., Gibney, M.J., 2001. The North/South Ireland Food Consumption Survey: survey design and methodology. Public Health Nutr. 4, 1037–1042. https://doi.org/10.1079/phn2001184

IUNA (Irish Universities Nutrition Alliance), 2005. National Children's Food Survey. Main report. Iuna Survey Reports Dietary Research Nutritional Research.

Li Shiyou, Yuan Wei, Deng Guangrui, Wang Ping, Yang Peiying,, Aggarwal Bharat, 2011. Chemical Composition and Product Quality Control of Turmeric (Curcuma longa L.). Pharm. Crops 5, 28–54. https://doi.org/10.2174/2210290601102010028

Tennant D., 2007. Screening potential intakes of natural food colours. Report provided for the Natural Food Colours Association (NATCOL).

Tennant D., 2006. Screening of Colour Intakes from Non-Alcoholic Beverages. Report prepared for the Union of European Beverages Associations (UNESDA), December 2006.