This is a draft statement for discussion.
It does not reflect the final views of the Committee and should not be cited.

TOX/2019/74

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft statement on the safety of turmeric and curcumin.

Introduction

1. 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. For centuries, turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases (Ammon & Wahl 1991).

2. Many of the pharmacological properties of turmeric have been attributed to curcumin, hereafter referred to as diferuloylmethane. These properties include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities (Alok et al. 2015). Diferuloylmethane is a polyphenol compound naturally present within turmeric rhizomes. Its derivatives demethoxycurcumin and bisdemethoxycurcumin are also present within turmeric rhizomes. These compounds are collectively called “curcuminoids”

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

4. The Food Standards Agency has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of the new outbreaks and due to the uncertainties surrounding the composition and possible contamination of these commodities, the Committee on Toxicity (COT) has been asked to comment on the risk to human health from turmeric and curcumin in their various forms.

5. A discussion paper (TOX/2019/52) was presented to the Committee providing information on the information available on the safety of curcumin in supplements and past raw turmeric contamination issues, particularly in relation to lead. The current statement expands on exposure to raw and powdered turmeric both in the diet and as used in higher quantities for their purported health benefits.

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Questions on which the views of the Committee are sought

i). The Members are invited to comment on structure and content of the draft statement.

Secretariat

November 2019

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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

First draft statement on safety of turmeric and curcumin.

Introduction

1. Turmeric is a commonly used culinary spice. For centuries, turmeric has been widely used for imparting colour and flavour to food, and in Indian and Chinese traditional medicine as a remedy for the treatment of inflammation and other diseases (Ammon & Wahl 1991).

2. Many of the pharmacological properties of turmeric have been attributed to curcumin. 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 demethoxycurcumin and bisdemethoxycurcumin are also present within turmeric rhizomes. These compounds are collectively called “curcuminoids”

3. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, in recent months there has been an increase in numbers for reports of hepatotoxicity linked to the consumption of curcumin supplements.

4. 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 3mg/kg bw/d had been established by JECFA in 2004 based on a reproductive toxicity study and this was re-confirmed in the evaluation by EFSA in 2010.

5. The FSA’s Novel Foods Team consider turmeric food supplements comprising of turmeric oleoresin extract[1] or pure curcumin powder to be novel. These products were not significantly used as a food or food ingredient before 15th of May 1997. Therefore, before these products may be placed on the market in the EU as a food supplement, a safety assessment under the Novel Food Regulation is required.

[1] Turmeric powder extracted with organic solvents.

6. Supplement intake leads to exposures that are several magnitudes higher than the ADI. Furthermore, synthetic forms of turmeric and curcumin or conjugation with other chemicals such as piperine are used to increase absorption, thus altering its toxicokinetic profile.

7. 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. Italy's National Institute of Health the interdisciplinary group, section dietetics, and the technical committee for animal nutrition and health concluded that, to date, the causes are likely to be related to individual susceptibility, pre-existing alterations, latent hepato-biliary function or even the use of drugs". The Institute adopted a warning for the labelling of the supplements in question (to take effect from 31st December 2019), advising against their use for subjects with altered hepato-biliary function, and recommending medical advice when other medications are being taken

Background

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

9. Curcumin (E 100) is a dicinnamoylmethane dye authorised as a food additive in the EU for use in beverages and foodstuffs according to the European Parliament and Council Directive 94/36/EC[2]. It has been evaluated by the JECFA, SCF and EFSA. An ADI of 3 mg/kg bw/d had been established based on a reproductive toxicity study by JECFA in 2004 and was re-confirmed in the evaluation by EFSA in 2010.

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

11. Intake of some supplements leads to exposures that are several magnitudes higher than the ADI. Naturally curcumin has low oral bioavailability, due to its hydrophobic nature. However, in supplements, synthetic forms of curcumin and conjugation with other chemicals such as piperine are used to increase absorption, thus altering its toxicokinetic profile.

12. Contamination of turmeric has been a health and safety issue in the past. Contamination with lead is a result of either turmeric grown on lead rich soil or intentional adulteration with lead chromate. Often lead chromate, a lead-based colour, is used to enhance the appearance of turmeric. As a

[2] OJ L 273, 10.9.94, p.13

result, raw or ground turmeric could potentially contain high levels of lead. Turmeric powder can be adulterated with powders of other species of Curcuma (Reyma et al. 2004) which may be toxic. For example, the powder of Curcuma zedoaria, a common adulterant in turmeric powder, is known to be toxic; the high-protein flour of C. zedoaria caused 100 % mortality within 6 days when given at 320 g/kg diet to 5 week-old rats (Latif et al. 1979).

13. In supplements, a number of reported cases involved adulteration with nimesulide, a nonsteroidal anti-inflammatory drug known to cause liver problems.

Supplements and reported hepatotoxicity

14. Between December 2018 and 20th July 2019, a total of 21 individual cases of acute cholestatic hepatitis "likely to be linked to the consumption of food supplements based on curcumin and piperine" were reported on Italian territory. A total of 18 turmeric supplements have been associated with the outbreak. [3]. A total of 18 turmeric supplements have been associated with this hepatitis outbreak, one of which ("Curcuma Liposomal & black pepper" by Nutrimea) was recalled by Belgium's Federal Agency for Food Chain Safety (AFSCA) [4].

15. Whilst the AFSCA said that "the exact source of contamination had not yet been established", an update from Italy's National Institute of Health indicated that "the interdisciplinary group, section dietetics, and the technical committee for animal nutrition and health concluded that, to date, the causes are likely to be related to individual susceptibility, pre-existing alterations, latent hepato-biliary function or even the use of drugs". The Institute adopted a warning for the labelling of the supplements in question (to take effect from 31st December 2019), advising against their use for subjects with altered hepato-biliary function, and recommending medical advice when other medications are being taken. The Institute added that for turmeric powder, which was implicated in one hepatitis case, no particular recommendations were needed especially considering its history of consumption as a food.

16. The Food Standards Agency has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of the new outbreaks and due to the uncertainties surrounding the composition and possible contamination of these commodities, the Committee on Toxicity (COT) has been asked to comment on the risk to human health from turmeric and curcumin in their various forms.

Toxicokinetics

[3] https://www.nutraingredients.com/Article/2019/07/26/Italy-rejects-contamination-as-hepatitis-cause-citing-individual-susceptibility

[4] https://www.nutraingredients.com/Article/2019/07/11/Belgium-recall-same-curcumin-based-supplement-linked-to-Italian-hepatitis-cases

17. In both humans and animals curcumin, hereafter referred to as diferuloylmethane, has been shown to have low oral bioavailability.

18. Approximately 75% of the administered dose was excretes in the faeces with negligible amounts appearing in the urine following oral administration of 1g/kg bw of curcumin in rats (Wahlstrom & Blennow 1978). Oral bioavailability is similarly low in humans, due to poor absorption and extensive first-pass metabolism in the intestine and liver (Ireson et al. 2001, 2002).

19. Numerous studies have evaluated the level of curcumin after administration and found that either no curcumin or its metabolites, or only low levels, were detected in serum or tissue (Shen and Ji, 2012). Ravindranath & Chandrasekhara (1981) evaluated the tissue distribution of “curcumin” using tritium-labelled drug in male Wistar rats. They found that radioactivity was detectable in blood, liver, and kidney following doses of 10, 80, or 400 mg of $^{[3H]}$curcumin. With 400 mg, considerable amounts of radiolabelled products were present in tissues 12 days after dosing. The percentage of curcumin absorbed (60-66 % of the given dose) remained constant regardless of the dose indicating that administration of more curcumin does not result in higher absorption. Shoba et al. (1998) orally administered 2 g/kg bw curcumin to rats and reported the absorption and elimination half-lives to be 0.31 ± 0.07 and 1.7 ± 0.5 hours, respectively.

20. In humans, the same dose of curcumin did not allow the calculation of these half-life values because the serum curcumin levels were below the detection limit at most of the time points in most of the experimental subjects.

21. In supplements, however, it is common practice to alter curcumin metabolism to enhance its bioavailability. This can be achieved with methods such as the use of liposomal curcumin, curcumin nanoparticles, the use of curcumin phospholipid complex and the use of structural analogues of curcumin that are water soluble. The use of adjuvants that interfere with glucuronidation is also popular. For example, piperine, the major active ingredient in black pepper, has been shown to increase the bioavailability of curcumin by up to 2000% (Hewlings & Kalman, 2017).

Toxicity

Derivation of a Health Based Guidance Value

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

23. In 1996, JECFA evaluated the results of toxicology and carcinogenicity studies in rats and mice administered turmeric oleoresin containing 79-85 % curcuminoids (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 the NOAEL of 220 mg/kg bw/day in the carcinogenicity study of mice and a safety factor of 200, JECFA increased the temporary ADI to 0-1 mg/ kg bw and extended it, pending the submission of the results of a reproductive toxicity study with curcumin (JECFA, 1996).

24. 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 significant decreases in the average bodyweights of Wistar rat F2 generation pups (JECFA 2004).

25. In 2010, EFSA 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 2010). Wistar rats were fed diets containing diferuloylmethane (> 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.

26. Significant decreases in the average weights of the F2 generation pups were observed at days 1 and 7 at the intermediate dose, and on days 7, 14 and 21 at the high dose. These decreases represented < 10 % of the average weight of the concurrent controls and were reported to be within the range of the historical control data. There were no other effects on general health, body weight, pup survival or fertility indices in either generation. JECFA considered the effect on pup weight seen at the intermediate dose (equal to 250-320 mg/kg bw/day) to be incidental and therefore a NOEL. JECFA allocated an ADI for curcumin of 0-3 mg/kg bw/day based on the application of an uncertainty factor of 100 to this NOEL (JECFA 2004).

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

Hepatitis

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

instead of being eliminated in the bile. The liver has a remarkable ability to regenerate after damage but often fails to replicate the original complex cellular architecture necessary for normal function and instead produces cirrhosis, a combination of fibrous tissue and regenerative nodules.

29. In the UK, the most common causes of liver injury are fatty infiltration of the liver or viral infection, but toxicants (including alcohol), genetic storage disease and autoimmune processes can also lead to liver damage. In a proportion of patients, no ready explanation can be found for liver damage however severe. Toxicant-induced hepatitis, usually caused by drugs, is common and often resolves when the relevant chemical exposure ceases. In some cases, however, cellular damage is severe and the outcome can be fatal.

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

Morphology of hepatitis

31. The morphological appearances of different types of hepatitis are often similar (Ferrell, 2001). Pathological features of acute hepatitis include swelling and ballooning of hepatocytes and cell death 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.

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

Idiosyncratic drug hepatotoxicity

33. Idiosyncratic drug hepatotoxicity (IDH) occurs in1/500 to 1/50,000 individuals exposed to a particular drug (the prevalence of idiopathic hepatitis in the community is estimated to be 1/100,000) (Kaplowitz, 2005). IDH has been associated with a variety of pharmaceutical drugs as well as food supplements, notably kava kava. IDH is generally too rare to be detected in clinical trials, though elevated ALT levels may be an indicator. As a general rule, an ALT level greater than three times the upper level of normal is considered to be a sensitive indicator of liver toxicity (the marker is not completely specific since muscle injury may elevate ALT levels). While this is nearly universally described for idiosyncratic liver toxicants, it is not always predictive of overt idiosyncratic toxicity.

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

Turmeric and hepatotoxicity

Animal studies

Subacute toxicity

Rats

35. Liju *et al.* (2013) investigated the acute and sub-chronic toxicity of turmeric essential oil (TEO) from *Curcuma longa* L. Acute administration of TEO was done as a single oral dose of up to 5 g/kg bw, and a 13-week sub-chronic toxicity study was done at doses of 0.1, 0.25 and 0.5 g/kg bw/day in Wistar rats. There were no 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.

Mice

36. Dietary turmeric powder (0.2 %, 1.0 %, 5.0 %, equivalent to 400, 2000, 10000 mg/kg bw/day) or ethanolic turmeric extract (ETE, 0.05 %, 0.25 %, equivalent to 100, 500 mg/kg bw/day) for 14 days, at doses reported to be cancer preventive in model systems, were found to be hepatotoxic in mice. The diferuloylmethane contents of the turmeric powder and ETE were not reported. Exposure of mice to dietary turmeric or ETE did not have any significant effect on body weight/ liver weight or liver to body weight ratios. Animals exposed to 0.2 % turmeric showed coagulative necrosis in liver. Livers from mice receiving 1.0 % and 5.0 % turmeric showed extreme

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

Sub-chronic toxicity

Mice

37. 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) showed a significant reduction in body weight gain, alterations in absolute and/ or relative liver weights, and hepatotoxicity i.e. focal necrosis or focal necrosis with regeneration both in mice and rats. In mice, lower doses of turmeric (i.e. 0.2 or 1 % for 14 days) also showed hepatotoxicity and they were found to be more vulnerable to turmeric-induced hepatotoxicity than rats. (Deshpande *et al*. 1998).

38. In a 13 week study, groups of 10 male and 10 female $B6C3F_1$ mice were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin, which were estimated to deliver average daily doses of 150, 750, 1700, 3850, or 7700 mg/kg bw to males and 200, 1000, 1800, 4700 or 9300 mg/kg bw to females (NTP 1993). The major component of the oleoresin was identified as diferuloylmethane (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. Clinical findings in mice included stained fur, and discoloured faeces and urine. According to NTP, there were no biologically significant differences in hematologic, clinical chemistry, or urinalysis parameters, and there were no chemical related histopathologic lesions. EFSA (2010) concluded that the no-

effect level with respect to gross and microscopic pathological changes was 7700 and 9280 mg/kg bw/day in males and females, respectively, which were the highest doses tested.

Rats

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

40. In a 13 week study, groups of 10 male and 10 female F344/N rats were fed diets containing 0, 1000, 5000, 10000, 25000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane), estimated to deliver average daily doses of 50, 250, 480, 1300, or 2600 mg/kg bw to males and 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, 10000, 25000, and 50000 ppm were significantly greater than those of the controls. According to NTP, these increases may have been due to mild hepatocellular swelling or hypertrophy. In the clinical chemistry, urinalysis, and other hematologic parameters, 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. (NTP 1993).

41. 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 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 sacrifice. It was found that 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 the group of male animals receiving 250 mg/kg bw/day of curcuminoids, actual and relative liver weights

and the level of alkaline phosphatase (ALP) were significantly higher than those of the two controls, but the ALP level was still within a normal range. There appeared to be a higher incidence of mild degree of liver fatty degeneration and adrenocortical fatty degeneration in this group of animals, however the incidence was not significantly different from that of the two controls. The authors concluded that at higher doses, curcumin may affect the function and morphology of the liver in a reversible manner. The EFSA Panel concluded that due to the lack of knowledge on the diferuloylmethane content and nature of the extract tested, the study could not be used to assess the safety of diferuloylmethane. (Chavalittumrong *et al.* 2002).

Chronic toxicity

2-year study in rats

42. Groups of 60 male and 60 female F344/N rats were fed diets containing 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane) for 104 (males) or 103 (females) weeks, which were estimated to deliver average daily doses of 80, 460, or 2000 mg/kg bw to males and 90, 440, or 2400 mg/kg bw to females. Nine or 10 rats from each exposure group were evaluated after 15 months. Survival of exposed male and female rats was similar to that of the controls. The final mean body weights of all exposed male rats and female rats receiving 2000 and 10000 ppm were similar to those of the controls. The final mean body weights of male and female rats that received 50000 ppm were slightly lower (up to 10 %) than those of the controls throughout much of the study. Feed consumption by exposed male and female rats was similar to that by 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. (NTP 1993).

2-year study in mice

43. Groups of 60 male and 60 female B6C3F_1 mice were fed diets containing 2000, 10000, or 50000 ppm turmeric oleoresin (79 to 85 % diferuloylmethane) for 103 weeks, which were estimated to deliver average daily doses of 220, 520, or 6000 mg/kg bw to males and 320, 1620, or 8400 mg/kg bw to females (NTP 1993). Nine or ten mice from each exposure group were evaluated after 15 months. Survival of exposed male and female mice was similar to that of the controls (male: 0 ppm, 43/50; 2000 ppm, 43/50; 10000 ppm, 37/50; 50000 ppm 42/50; female: 39/50, 41/50, 34/50, 42/50). 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 by the controls throughout the study. The absolute and relative liver weights of male and female mice receiving 10000 and 50000 ppm were significantly greater than those of the controls at the 15-month interim evaluation. There were no clinical findings related to toxicity. No biologically significant differences were observed in hematologic parameters. The alkaline phosphatase values of male and female mice that received 10000 and 50000 ppm were significantly higher than those of controls at the 15-month interim evaluation. The incidences of hepatocellular adenoma in male and female mice receiving 10000 ppm (the mid dose group), but not those in mice receiving 2000 or 50000 ppm, were significantly increased (male: 25/50, 28/50, 35/50, 30/50; female: 7/50, 8/50, 19/51, 14/50). The number of male and female mice in the 10000 and 50000 ppm groups with multiple hepatocellular neoplasms compared with controls was of statistical significance. However, JECFA concluded that this effect was not dose-related and that curcumin is not a carcinogen (JECFA 1996). In addition, the EFSA Panel noted that all statistically significant effects noted by the NTP refer to benign neoplastic lesions (adenomas) (EFSA 2010). 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 $B6C3F_1$ mice are not relevant for humans. Therefore, the Panel agreed with JECFA that curcumin is not carcinogenic.

Case studies in humans

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

45. In Australia, 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 Ancient Wisdom Modern Medicine High Potency Turmeric (375 mg curcuminoids and 4 mg black pepper per tablet), along with a flaxseed oil supplement and occasional diclofenac use for arthritic pain. (*N.B.* this supplement leads to an intake of 204.6 % of the ADI of 3 mg/kg bw/day, see Table 5). 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.

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

47. 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 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 (1125 mg curcuminoids per day) 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.

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)*.

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

49. In the US, 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 aspartate aminotransferase 1553 mg/dL, alanine aminotransferase 2607 mg/dL, alkaline phosphatase 246 mg/dL and total bilirubin 1.6 mg/dL with a direct component of 1 mg/dL. Hepatic synthetic function was intact. Medications included naproxen and ergocalciferol (vitamin D) with no changes four years prior to the onset of transaminitis. Viral infections were ruled out. Autoimmune work-up yielded positive antinuclear antibody (1:250) with normal anti-smooth muscle antibody and serum IgG levels. Abdominal Doppler was negative for portal or hepatic

vein thrombosis. Magnetic resonance cholangiopancreatography did not show any biliary ductal pathology. It was discovered that the patient was taking turmeric supplements for 6 months. A liver biopsy demonstrated panlobular 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.

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

51. 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.

52. Subsequent reassessment of the liver biopsy by the authors 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 here 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.

Exposure

Exposure from use in food

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

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

Curcuminoid	**Composition in turmeric powders (mean) (% dry weight)**	**Composition in turmeric oleoresin extracts (mean ± s.d.)** **(% dry weight)**
Diferuloylmethane	2.86	19.51 ± 2.07
Demethoxycurcumin	1.47	8.31 ± 1.13
Bisdemethoxycurcumin	1.36	6.22 ± 0.88
Total	5.69	34.04 ± 4.08

54. 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. diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin) (EC 2008). Moreover, JECFA (1992) stated that “purified extracts of turmeric containing more than 90 % total colouring matter are subject to specifications for ‘Curcumin’”(JECFA 1992). EFSA (2010) noted that the specification should be updated to define the composition of the remaining 10 %, which may be accounted for by minor amounts of turmeric essential oil. Directive 94/36/EC states the maximum permitted levels (MPLs) for E100 in foodstuffs (which range from 20 to 500 mg/kg depending on the food item) and beverages (which range from 100-200 mg/L) (EC 1994).

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

56. For adults (> 18 years old), the EFSA Panel 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 NDNS, 2000-2001) are available (Tennant 2006,

2007). For children (1-10 years old), the Panel estimated exposure based on 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 2006, 2007).

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

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

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

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

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

(13-52 %), non-alcoholic beverages (15-57 %) and sauces and seasonings (11-45 %).

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

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

	Adult (18-64 years old) diferuloylmethane exposure (mg/kg bw/day)	**Children (5-12 years old) diferuloylmethane exposure (mg/kg bw/day)**
Exposure from spice added to food *		
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 *		
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 2005). The dietary intake of curry powder was also considered, as turmeric powder is a widespread ingredient in it (approximately 30 % depending on the blend).

60. The above information is indicative of the current exposures to curcumin and/or turmeric as part of the diet (food colour and as 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[5], it is proposed that to benefit from turmeric's antioxidant effects, one should consume between 500 to 1000 mg of curcuminoids per day. It is suggested that one teaspoon of fresh or powdered turmeric contains 200 mg of curcumin. Consumptions at the proposed levels, would lead to exposures to curcumin between 7.1 mg/kg bw/d and 14.3 mg/kg bw/d for a 70 kg adult, leading to exceedances up to 477% of the ADI. Using EFSA's default bodyweights, exposures in infants, children and adolescents would range from 42 mg/kg bw/d (1400% of ADI) to 83 mg/kg bw/d (2767% of ADI) for toddlers aged 1-3 and 8.2 mg/kg bw/d (273% of ADI) to 16mg/kg bw/d(533% of ADI) for adolescents aged 14-18 years old.

[5] https://www.wellandgood.com/good-food/turmeric-anti-inflammatory-dosage/

Exposure through turmeric supplements

61. In addition to exposure to diferuloylmethane through a normal diet, turmeric supplements can also be taken.

62. Curcuminoids can be extracted from ground turmeric powder using organic solvents to create a turmeric oleoresin extract (Table 2). JECFA (1992) lists several solvents permitted for extraction: acetone, methanol, ethanol, and isopropanol. The European Commission, however, has a different list of permitted solvents: acetone, carbon dioxide, ethyl acetate, dichloromethane, n-butanol, methanol, ethanol, and hexane (EC 2008). According to JECFA specifications, residual solvent concentrations in turmeric oleoresin intended for use in food are limited to 25 mg/kg for hexane, 30 mg/kg for acetone, dichloromethane, and 1,2-dichloroethane, and 50 mg/kg for ethanol, methanol, and isopropanol (JECFA 1992). 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 (Table 4).

Table 4: *Preparation and composition of turmeric products that are commercially available as dietary supplements (adapted from Li et al. 2011).*

Commercial product name	***Preparation***	***Composition***
Turmeric powder	*Prepared from dried rhizomes of C. longa*	*0.58-3.14 % diferuloylmethane (dry weight), and other curcuminoids*
Turmeric oleoresin extract	*Treat turmeric powder with organic solvents*	*37-55 % curcuminoids, < 25 % essential oil*
Turmeric oil extract	*Treat turmeric powder with steam distillation or supercritical CO_2 extraction*	*Essential oil from leaves usually dominated by monoterpenes whilst oil from rhizomes mainly contains sesquiterpenes*
Curcumin powder	*Purify turmeric oleoresin through crystallisation*	*> 90 % curcuminoids, and minor amounts of essential oil*

63. Whilst curcuminoids are responsible for the yellow-orange colour of turmeric, it is the volatile sesquiterpenes present in the rhizome's essential oil that are responsible for its aroma and taste (Li et al. 2011). The major sesquiterpenes in turmeric oil extract are α-, β-, and Ar-turmerone (Li et al. 2011), which can together account for > 40 % of the essential oil present in

turmeric rhizomes (Stanojević et al. 2015). Turmerone possesses diverse pharmacological activities that include antioxidant and antimutagenic activities (Jayaprakasha et al. 2002). Turmeric oil extract can be prepared in various ways, for example through the treatment of turmeric powder with steam distillation, supercritical CO_2 extraction (Li et al. 2011), or by evaporating the organic solvent of a crude turmeric oleoresin extract (Funk et al. 2010) (Table 2).

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

65. Ground turmeric powder, turmeric oleoresin extract and diferuloylmethane powder are the compositions of turmeric that contain diferuloylmethane and which can be taken as supplements. A selection of these supplements (which can be readily purchased on the internet) are presented in Table 5, where the contribution of daily supplemental intake of diferuloylmethane to the ADI of 3 mg/kg bw/ day is calculated, with and without dietary diferuloylmethane. Of the supplements presented in Table 5, those containing ground turmeric powder do not exceed the ADI of 3 mg/kg bw/day for diferuloylmethane, either alone or with dietary intake of diferuloylmethane. Conversely, supplements comprising of turmeric oleoresin extract generally do lead to an exceedance of the ADI.

66. The FSA's Novel Foods Team consider turmeric food supplements comprising of turmeric oleoresin extract or pure curcumin powder to be novel. These products were not significantly used as a food or food ingredient before 15th of May 1997. Therefore, before these products may be placed on the market in the EU as a food supplement, a safety assessment under the Novel Food Regulation is required.

Table 5: The contribution of some commercial turmeric supplements to the dietary ADI for diferuloylmethane.

Commercial product name	**Main ingredient(s)**	**Daily dosage recommended on vendor website**	**Diferuloylmethane intake (mg/ kg bw day) (supplement**	**% ADI of 3 mg/kg bw/day**	**% ADI of 3 mg/kg bw/day**

			only) *	**(supplement only)**	**(supplement & diet)** ‡
Prowise Organic Turmeric Max Strength (Prowise Healthcare)	Turmeric powder, black pepper	1 capsule, each containing 600 mg turmeric powder	0.25	8.2 †	41.7
Nature's Garden Turmeric 400mg (Holland and Barrett)	Turmeric powder	2 capsules, each containing 400 mg turmeric powder	0.33	10.9	44.3
Turmeric Curcumin Supplement with Bioperine® (Primal Living)	Turmeric powder, Bioperine®	1-2 tablets, each containing 500 mg turmeric powder	0.41	13.6 †	47.0
Maxsorb Turmeric (Simply Supplements)	Turmeric powder, piperine	2 capsules, each containing 500 mg turmeric powder	0.41	13.6 †	47.0
Organic Turmeric (Curcumin) + Black Pepper Strong 600mg Capsules (Health Essentials)	Turmeric powder, BioPerine®	2 capsules, each containing 600 mg turmeric powder	0.49	16.3 †	49.7
Opti-Turmeric capsules (HealthSpan)	NovaSOL® curcumin (containing turmeric extract)	1-2 capsules, each containing 30 mg curcuminoids	0.49	16.4 †	49.7
Organic Turmeric Curcumin 1380 mg with Organic Black Pepper & Organic Ginger (Vita Bright)	Turmeric powder, black pepper	2 capsules, each containing 630 mg turmeric powder	0.51	17.2 †	50.3
Swanson Turmeric (Healthy Monthly)	Turmeric powder	2 capsules, each containing 720 mg turmeric powder	0.59	19.6	53.0
Advanced Turmeric - Turmeric/Curcumin with Bioperine® (Black Pepper) (Autoimmune Institute)	Turmeric powder, BioPerine®	2-4 capsules, each containing 500 mg turmeric powder	0.82	27.2 †	60.7
Cell Active Curcumin Plus (Cytoplan)	Longvida® Optimised Curcumin	2 capsules, each containing 250 mg Longvida® Optimised Curcumin	1.8	59.5 †	93.3
Flexi6 Gold (HealthSpan)	Turmeric extract	2 tablets, each containing 126 mg curcuminoids	2.1	68.8	103.3
Turmeric Tablets 20,000 mg (Nature's Best)	Turmeric extract	1 tablet containing 475 mg curcuminoids	3.9	129.6	163.3

Turmeric 500mg 95% Curcumin (20:1 extract eq. 10,000mg) + Bioperine® (Zip Fit)	Turmeric extract, BioPerine®	1 tablet containing 475 mg curcuminoids	3.9	129.6 †	163.3
High Potency Turmeric (Ancient Wisdom Modern Medicine)	Turmeric extract, Bioperine®	1-2 tablets, each containing 375mg curcuminoids	6.1	204.6 †	236.7
Turmeric 500 mg (HealthSpan)	Turmeric extract	1-2 tablets, each containing 475 mg curcuminoids	7.8	259.2	293.3
Turmeric 10,000 with BioPerine® Black Pepper Extract (HealthSpan)	Turmeric extract, BioPerine®	1-2 tablets, each containing 475 mg curcuminoids	7.8	259.2 †	293.3
Turmeric Pro with BioPerine® 12,500mg 95% Curcuminoids (Evolution Slimming)	Turmeric extract, BioPerine®	2 capsules, each containing 475 mg curcuminoids	7.8	259.2 †	293.3
Curcumin (Turmeric) with Black Pepper - Powder Capsules (Supplement Place)	Turmeric extract, black pepper extract	2 capsules, each containing 750 mg curcuminoids	12.3	409.3 †	443.3
Turmeric + Bioperine® Tablets - 10,000mg)Just Vitamins)	Turmeric extract, BioPerine®	1-2 tablets, each containing 475 mg diferuloylmethane	13.6	452.4 †	486.7
Turmeric Curcumin Advanced Complex (Piping Rock Health Products)	Turmeric extract, black pepper extract	2-4 capsules, each serving of 2 capsules containing 1425 mg curcuminoids	23.5	783.1 †	816.7

* Calculated using adult body weight of 70 kg (EFSA 2012), and maximum recommended daily dosage. For turmeric powder, the calculation assumes 2.86 % is diferuloylmethane, e.g. (600 mg/day turmeric powder x 2.86 %) / 70 kg bw = 0.25 mg/kg bw/day. For turmeric oleoresin extract, calculation assumes 57.3 % of total curcuminoid content is diferuloylmethane (derived from Table 1). For Longvida® Optimised Curcumin, calculation assumes 25 % of the formulation is diferuloylmethane (Gota *et al.* 2010).

† Product formulation or composition expected to enhance bioavailability of diferuloylmethane.

‡ Assumes a mean contribution of 1.0 mg/kg bw/day diferuloylmethane from the diet for adults (see Table 3).

Risk Characterisation

67. For raw and powdered turmeric/curcumin, consumption as part of the normal diet (from its use as an additive and spice) would lead to exposures

that are generally within the ADI, apart from the high consumers group for children (Table 3). However, these exposures are conservative as the maximum reported levels were used for intake estimation. Generally, intake from the normal diet amounts to less than 7% of the ADI of 3 mg/kg bw/day (EFSA, 2010).

68. There is high uncertainty regarding the risk for the intake of raw and powdered turmeric in high quantities for their purported health benefits. The literature review of human studies suggests oral diferuloylmethane in humans is well tolerated up to doses of 114 mg/kg bw/day, though minor symptoms of nausea or diarrhoea may occur. Long-term studies are lacking, however.

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

70. Lead in the body is distributed to the brain, liver, kidney and bones. It is stored in the teeth and bones, where it accumulates over time. Human exposure is usually assessed through the measurement of lead in blood. Lead in bone is released into blood during pregnancy and becomes a source of exposure to the developing fetus (WHO, 2017).

71. The Panel on Contaminants in the Food Chain (CONTAM Panel) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment. The respective BMDLs derived from blood lead levels in µg/L (corresponding dietary intake values in µg/kg bw/d) were: developmental neurotoxicity BMDL01, 12 (0.50); effects on systolic blood pressure BMDL01, 36 (1.50); effects on prevalence of chronic kidney disease BMDL10, 15 (0.63). The Panel highlighted that by protecting children, who are far more sensitive, from the developmental effects of lead, the general population would also be protected from any adverse effects from lead.

72. The FSA recently received an enquiry where a family had been consuming raw turmeric (grown on lead-rich Indian soil) for over a year; following a blood test, the enquirer tested positive for lead. The enquirer mentioned that the family's young toddler had also been exposed to the contaminated turmeric.

73. It is impossible to be able to determine the risk to human health without analytical results from the contaminated batches of turmeric, that would allow for a quantitative risk assessment to be performed.

74. With regard to supplements, exposure assessment for dietary turmeric supplements indicates substantial exceedances of the ADI can occur for diferuloylmethane, which are generally for the supplements containing turmeric extracts. Furthermore, these supplements are generally modified to increase the bioavailability of curcumin, which could potentially alter the

toxicity profile of the chemical. As mentioned previously, information on the long term toxicity of curcumin is lacking, however safety margins are being eroded, meaning that the risk of adverse effects, particularly, in vulnerable individuals is increased.

75. Based on the available information from both animal and human studies, it appears that there is a link to turmeric because the effects occurred upon challenge and were reversed after withdrawal. The symptoms are considered to be an idiosyncratic drug reaction. However, a role for a possible contaminant cannot be ruled out. The animal data is consistent with the human data.

Conclusions

76. 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.

77. 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 and the European Food Safety Authority (EFSA). An ADI of 3 mg/kg bw/d had been established based on a reproductive toxicity study by JECFA in 2004 and was re-confirmed in the evaluation by EFSA in 2010.

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

79. Curcumin has low bioavailability, however in supplements synthetic forms of curcumin or chemical alterations are used to increase its bioavailability by up to 2000%, thus potentially altering its toxicity profile.

80. Consumption of turmeric/curcumin as part of the diet from its use as a food additive or as spice generally leads to exposures that are below the ADI. However, when consumed in high quantities for its purported health benefits, or via the intake of supplements, substantial exceedances of the ADI can occur. There is lack of information on the chronic toxicity of turmeric/curcumin thus the risk to health cannot be determined. Moreover, there is known contamination issues in turmeric, particularly with lead that are also associated with adverse health effects. However, due to the lack of analytical data the risk to health cannot be determined.

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

82. The Committee agreed substantial exceedances of the ADI represent a potential health risk to humans, especially if other medicines are being taken concomitantly.

83. Given past reported contamination issues with turmeric supplements, the Committee concluded that there would be value in commissioning a chemical analysis of turmeric supplements and raw/powdered turmeric available on the UK market.

Secretariat

November 2019

This is a draft statement for discussion.
It does not reflect the final views of the Committee and should not be cited.

Abbreviations

µg/kg bw/d -	Micrograms per kilogram bodyweight per day
ADI -	Acceptable Daily Intake
AFSCA -	Belgium's Federal Agency for Food Chain Safety
ALT -	Alanine Aminotransferase
ASP -	Alkaline Phosphatase
AST -	Aspartate Aminotransferase
CONTAM -	Panel on Contaminants in the Food Chain
COT -	Committee on Toxicity
EFSA -	Scientific Committee on Food and the European Food Safety Authority
ETE -	Ethanolic Turmeric Extract
EXPOCHI -	Exposure Assessments For Children In Europe
IDH -	Idiosyncratic Drug Hepatotoxicity
JECFA -	Joint FAO/WHO Expert Committee on Food Additives
LFT -	Liver Function Test
mg -	Milligram
mg/kg bw/d -	Milligrams per kilogram bodyweight per day
MPL -	Maximum Permitted Levels
SBB -	Sudan Black B
SCF -	Scientific Committee on Food
TEO -	Turmeric Essential Oil

References:

Alok A., Singh I.D., Singh S., *et al.* (2015) Curcumin – Pharmacological Actions And its Role in Oral Submucous Fibrosis: A Review. *Journal of Clinical and Diagnostic Research* **9:** 1-3

Ammon H.P. & Wahl M.A. (1991). Pharmacology of Curcuma longa. *Planta Medica* **57:** 1-7

Braga M.E.M., Leal P.F., Carvalho J.E., *et al.* (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

Chavalittumrong P., Chivapat S., Rattanajarasroj S., *et al.* (2002). Chronic toxicity study of curcuminoids in rats. The Songklanakarin *Journal of Science and Technology* **24:** 633-647

Deshpande S.S., Lalitha V.S., Ingle A.D., *et al.* (1998) Subchronic oral toxicity of turmeric and ethanolic turmeric extract in female mice and rats. *Toxicol Lett* **95:** 183-193

EC (1994) European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs. OJ L 273, 10.9.94 Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31994L0036&from=EN

EC (2008) European Commission Directive 2008/128/EC Laying down specific purity criteria concerning colours for use in foodstuffs. OJ L 6, 10.1 p. 20-63. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32008L0128

EFSA (2010) EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive. *EFSA Journal* **8:** 1679

EFSA (2012) Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. *EFSA Journal* **10:** 2579

Ferrell, L. (2001) Liver Pathology:Cirrhosis, Hepatitis, and Primary Liver Tumours. Update and Diagnostic Problems. *Modern Pathology* **13**: 679-704

Funk J.L., Frye J.B., Oyarzo J.N., *et al.* (2010) Anti-Arthritic Effects and Toxicity of the Essential Oils of Turmeric (Curcuma longa L.) *J Agric Food Chem.* **58:** 842-849

Gota V.S., Maru G.B., Soni T.G., *et al.* (2010). Safety and Pharmacokinetics of a Solid Lipid Curcumin Particle Formulation in Osteosarcoma Patients and Healthy Volunteers. *J. Agric. Food Chem.* **58:** 2095-2099

Harrington K.E., Robson P.J., Kiely M., *et al.* (2001). The North/South Ireland Food Consumption Survey: survey design and methodology. *Public Health Nutrition* **4:** 1037-1042

Hewlings S.J. & Kalman D.S. (2017) Curcumin: A Review of Its' Effects on Human *Health Foods* **6:** 92

Ireson C.R., Orr S., Jones D.J., *et al.* (2001) Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. *Cancer Res* **61:** 1058-64

Ireson C.R., Jones D.J., Orr S., *et al.* (2002) Metabolism of the cancer chemopreventive agent curcumin in human and rat intestine. *Cancer Epidemiol Biomarkers Prev* **11:** 105-11

IUNA (Irish Universities Nutrition Alliance) (2005). National Children's Food Survey. Main report: https://www.iuna.net/surveyreports

Jayaprakasha G.K., Jena B.S., Negi P.S., et al. (2002). Evaluation of antioxidant activities and antimutagenicity of turmeric oil: a byproduct from curcumin production. *Zeitschrift für Naturforschung C* **57:** 828-835

JECFA (1992) FNP 52: Turmeric Oleoresin. Available at: http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-484.pdf

JECFA (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. Available at:
https://apps.who.int/iris/bitstream/handle/10665/37246/WHO_TRS_859.pdf

JECFA (2004). 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. Available at:
http://whqlibdoc.who.int/trs/WHO_TRS_922.pdf

Kandarkar S.V., Sawant S.S., Ingle AD, *et al.* (1998) Subchronic oral hepatotoxicity of turmeric in mice-histopathological and ultrastructural studies. *Indian J Exp Biol* **36:** 675-659

Kaplowitz, N. (2005) Idiosyncratic Drug Hepatotoxicity. *Nat Rev Drug Discov*, **4**: 489-499

Latif M.A., Moris T.R., Miah A.M., *et al.* (1979) Toxicity of shoti (Indian arrowroot: Curcuma zedoaria) for rats and chicks. *Br. J. Nutr.* **41:** 57-63.

Li S., Yuan W., Deng G., *et al.* (2011) Chemical composition and product quality control of turmeric (Curcuma longa L.). Faculty Publications. Paper 1. Available at: https://core.ac.uk/download/pdf/72733173.pdf

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 and Chemical Toxicology* **53:** 52-61

Luber R.P., Rentsch C., Lontos S., *et al.* (2019). Turmeric Induced Liver Injury: A Report of Two Cases. *Case Reports in Hepatology* doi: 10.1155/2019/6741213.

Lukefahr A.L., McEvoy S., AlfafaraC., *et al.* (2018) Drug-induced autoimmune hepatitis associated with turmeric dietary supplement use. *BMJ Case Rep* doi: 10.1136/bcr-2018-224611

National Toxicology Program (NTP). 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. Available at: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr427.pdf

Olojede A.O., Nwokocha C.C., Akinpelu A.O., *et al.* (2009) Effect of variety, rhizome and seed bed types on yield of turmeric (Curcuma longa L) under a humid tropical agro-ecology. *Adv. Bio.Res.* **3:** 40-42

Pfeiffer E., Hhle S., Solyom A.S., *et al.* (2003) Studies on the stability of turmeric constituents. *J. Food Engineer*. **56:** 257-259

Ravindranath V. & Chandrasekhara N. (1981) Metabolism of curcumin–studies with [^{3}H]curcumin. *Toxicology* **22:** 337-44

Remya R., Syamkumar S., and Sasikumar B. (2004) Isolation and amplification of DNA from turmeric powder. *Br. Food J.* **106:** 673-678

Sasikumar B. (2005) Genetic resources of Curcuma: diversity, characterization
and utilization. *Plant Gen. Resour.* **3:** 230-251

SCF (Scientific Committee for Food) (1975). Reports from the Scientific Committee for Food (1st series), opinion expressed 27 June 1975. Accessible via:
http://aei.pitt.edu/40814/1/food_1st.pdf

Shen L., Ji H-F. (2012) The pharmacology of curcumin: is it the degradation products? *Trends Mol Med*. 18(3):138–144.

Shoba G., Joy D., Joseph T., *et al.* (1998) Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* **64:** 353-6

Stanojević J.S. Stanojević L.P., Cvetković D.J., *et al.* (2015) Chemical composition, antioxidant and antimicrobial activity of the turmeric essential oil (Curcuma longa L.). *Advanced technologies* **4:** 19-25

Stierum R.A., Conesa A., Heihe W., *et al.* (2008). Transcriptome analysis provides new insights into liver changes induced in the rat upon dietary administration of the food additives butylated hydroxytoluene, curcumin, propylgallate and thiabendazole. *Food and Chemical Toxicology* **46:** 2616-28

Suhail F.K., Masood U., Sharma A., *et al.* (2019) Turmeric supplement induced hepatotoxicity: a rare complication of a poorly regulated substance. *Clinical Toxicology* DOI: 10.1080/15563650.2019.1632882

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

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

Wahlstrom B. & Blennow G. (1978) A study on the fate of curcumin in the rat. *Acta Pharmacol Toxicol* **43:** 86-92

WHO (2017): http://www.who.int/mediacentre/factsheets/fs379/en/