Toxicity

In this guide

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 BMDL01, 12 (0.50); increased systolic blood pressure (SBP) BMDL01, 36 (1.50); increased prevalence of chronic kidney disease BMDL10, 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).