Meeting

Annex A to TOX/2022/35

This is a draft statement for discussion.

It does not reflect the final views of the Committee and should not be cited.

Introduction

1. This annex contains information relating to past COT discussions on the safety of curcuminoids and turmeric. There is firstly a link to the most recent draft statement from March 2020. Secondly, there is a collation of relevant past COT minutes from discussions on the topic that took place in September 2019, December 2019, March 2020 and March 2022.

Second draft statement on the safety of turmeric and curcumin. (TOX/2020/13) (March 2020) Can be accessed

Tox-2020-12 Second Draft Statement Tumeric (food.gov.uk)

Previous minutes relating to COT discussions on the safety of turmeric

Minutes of the meeting held on Tuesday, 17th September 2019 in Broadway House Conference Centre, Tothill St, London, SW1H 9NQ – Item 8: Review of hepatotoxicity of dietary turmeric supplements- TOX/2019/52

2. Turmeric is the common name for the rhizome (underground stem) of Curcuma longa L., a 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. However, contamination of turmeric may occur either during its cultivation (if grown in lead-rich soil) or downstream processing where xenobiotics or powders of other Curcuma species may be introduced.

3. Over the last few years, a number of hepatitis outbreaks related to the consumption of dietary turmeric supplements have been reported. The paper reviewed some of the human case reports, in addition to studies of hepatotoxicity in animals.

4. One member noted that in the subacute study, the dietary turmeric powder the mice were administered may have been contaminated since in the published paper it was stated that these turmeric rhizomes were “purchased locally”.

5. It was noted that the human case studies showed a link to turmeric because the effects occurred upon challenge and were reversed after withdrawal. The symptoms were considered to be an idiosyncratic drug reaction due to underlying susceptibilities in the affected individuals. However, a role for a possible contaminant was not ruled out. It was concluded the animal data were consistent with the human data.

6. The Committee concluded that there was no need to review the current ADI for curcumin that was currently based on reproductive toxicity.

7. The Committee agreed substantial exceedances of the ADI represented a potential health risk to humans, especially if other medicines were being taken concomitantly.

8. Given past reported contamination issues with turmeric supplements, the Committee agreed there would be value in commissioning a chemical analysis of turmeric supplements available on the UK market.

Minutes of the meeting held on Tuesday, 3rd of December 2019 in the Amba Hotel Charing Cross, The Strand, London, WC2N 5HX - Item 11: Draft Statement on the safety of turmeric and curcumin - TOX/2019/74

9. No interests were declared.

10. 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, for centuries.

11. Many of the purported pharmacological properties of turmeric which include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities, have been attributed to curcumin, a compound naturally present within turmeric rhizomes.

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

13. The Food Standards Agency has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of recent reports 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.

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

15. The Committee discussed the first draft of the statement and agreed that, for clarity, the issue of hepatotoxicity from supplement intake should be discussed separately from the issue of contamination of raw/powdered turmeric with heavy metals, and therefore suggested restructuring the statement to reflect this.

16. Regarding supplement intake, the Committee questioned whether there was information available on the individual cases of hepatotoxicity related to intake of turmeric supplements and whether or not the cases could have been due to a localised issue with the supplements available in the Italian market. The Secretariat informed Members that at the time of preparing the statement information on the individual cases reported had not been located however should it become available it would be added to the second draft of the statement. It was noted that the Italian authorities had excluded contamination as a cause of the hepatotoxicity.

17. It was agreed that information on the sales and market share of turmeric/curcumin supplements should be included, to put into perspective the incidents of toxicity reported. Furthermore, Members noted that the increase in the incidents reported could be a reflection of the increase in the trend for consuming these supplements. Overall it was agreed that, based on the case studies presented, the effect is consistent with an idiosyncratic reaction, especially in people with underlying conditions such as latent impairment of biliary function. The Committee requested that the European Medicines Agency's conclusions of their review of curcumin be included in the statement and also for the text to reflect that effects in humans appear to occur at appreciably lower doses on a bodyweight basis than in experimental animals, where hepatocellular changes are observed only at high levels.

18. A number of amendments to the text were suggested and a revised draft statement would be brought to the March 2020 meeting.

Minutes of the meeting of the Committee held on 10th March 2020 at Manchester Conference Centre, Weston Building, Sackville Street, Manchester, Greater Manchester. Item 4: Safety of turmeric and curcumin: Second draft statement TOX/2020/13

19. No interests were declared.

20. 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 for centuries.

21. Many of the supposed pharmacological properties of turmeric have been attributed to curcumin, a compound naturally present within turmeric rhizomes. These properties are claimed to include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities.

22. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, a number of reports of hepatotoxicity linked to the consumption of curcumin supplements have been reported in Italy.

23. The FSA has been monitoring incidents related to consumption of raw and powdered turmeric and its supplements. In light of the reported cases and due to the uncertainties surrounding the composition and possible contamination of

these products, the COT was asked to comment on the risk to human health from turmeric and curcumin in their various forms.

24. The second draft statement addressed the recommendations made by the Committee on the first draft. These mainly related to separating the different issues of potential lead contamination, the effects of natural constituents and composition, particularly where designed to increase bioavailability.

25. Members made further recommendations on the structure and content of the statement including the need for a comment on current dietary exposure.

26. Members questioned the relevance of comparing exposures from supplement intake to the ADI for dietary curcumin. It was decided that it would not be appropriate because synthetic forms or adjuvated curcumin, which may be used in supplements, could have altered toxicokinetic profiles and increased bioavailability thus making the safe levels different from the forms used in food.

27. A number of amendments to the text were suggested by Members and it was agreed that a revised draft statement would be cleared by Chair’s action.

Minutes of the meeting held on Tuesday, 29th of March 2022 (Virtual attendance only) - Item 5: Discussion paper on the potential risk to human health of tumeric and curcumin supplements – following a recent product survey (TOX/2022/19)

28. Dr Stella Cochrane declared a non-personal specific interest as her employer Unilever produce and sell products containing turmeric. It was agreed this did not prevent her contributing to the discussion of this item.

29. 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 for centuries.

30. Many of the proposed pharmacological properties of turmeric have been attributed to curcumin, a compound naturally present within turmeric rhizomes. Properties proposed include antioxidant, analgesic, anti-inflammatory, antiseptic, anticarcinogenic, chemopreventive, chemotherapeutic, antiviral, antibacterial, antifungal and antiplatelet activities.

31. Due to its purported health benefits, the consumption of curcumin/turmeric supplements is increasingly popular. However, a number of reports of hepatotoxicity linked to the consumption of curcumin supplements were reported

in Italy. Turmeric was discussed by the Committee in September 2019 in paper TOX/2019/52 with first and second draft statements being considered in December 2019 (TOX/2019/74) and March 2020 (TOX/2020/13) respectively.

32. During discussions in September 2019, Members concluded that, given the past reported contamination issues with turmeric supplements, there would be value in commissioning chemical analysis of turmeric supplements available on the UK market.

33. Paper TOX/2022/19 presented the findings of a recent survey of turmeric supplements. The survey of 30 products was undertaken by Fera Science Ltd. All samples were analysed for the curcuminoids: curcumin, bisdemethoxycurcumin (BDMC) and demethoxycurcumin (DMC) as well as the black pepper derived alkaloid, piperine; and a comprehensive analysis of 69 trace elements which included the heavy metals lead (Pb), mercury (Hg), arsenic (As) and cadmium (Cd).

34. Members advised that where the recent EFSA opinion on tetrahydrocurcuminoids was briefly discussed in the paper, more detail may be needed in any subsequent statement to provide further context for these compounds. However, it was noted that although they may naturally occur in turmeric supplements, these transformation products of curcuminoids would potentially be covered by the novel food authorisation process, if isolated and used in supplements.

35. It was noted that in the section regarding the lead content of the supplements surveyed, the discussion after Table 6, should have referred to BMDL1 rather than BMDL10; further clarity over why this BMDL value was being used as a comparison against potential Pb exposure from taking the supplements analysed would be useful.

36. Members discussed the potential need to look further into supplements that have unusual or novel contents such as synthetic curcuminoids or where there were curcuminoids within nanoparticles, these products often claimed to have greater absorption. Further information such as market size and usage of these different types of supplements would be helpful if that could be obtained.

37. The Secretariat agreed to look further into the results on other metal concentrations generated as a result of this recent survey, in addition to the heavy metals considered in the discussion paper.

38. The Committee suggested some revisions to the emphasis of the discussion and conclusions on heavy metal contamination causing toxicity when discussing past incidents relating to turmeric supplements. A conclusion on the incident where several reports of hepatotoxicity linked to the consumption of curcumin supplements had been reported in Italy could be considered, as there was no evidence for heavy metal contamination in this incident.

39. Members requested further clarity when discussing hepatitis arising from drugs, to distinguish acute and chronic effects, and direct from idiosyncratic effects. Furthermore, when discussing idiosyncratic drug hepatotoxicity (IDH), to be clear that it is very much drug specific, i.e. many drugs can cause increases of ALT concentrations and the majority will not cause IDH.

40. Members requested some further detail be included regarding allergic IDH, in particular to explain why some people develop allergic IDH and others do not.

41. Members noted that the literature had not been reviewed since the topic had been last discussed by the Committee in 2020. This could be particularly relevant regarding the toxicokinetics of curcuminoids with adjuvant compounds such as piperine since the recent literature suggested that piperine levels in supplements may not increase the bioavailability of curcuminoids as previously thought.

42. It was suggested that further clarity be provided in the background section to link up the commentary describing turmeric supplements as a novel food and the approved use of curcumin as a food additive.

43. Members were informed that a further discussion paper or draft statement would be presented to the committee addressing the points discussed.