COC Evaluations

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26. 2024 Membership of the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment
27. Declaration of members interests during the period of this report - COC 2024

Hydroxyanthracene derivatives

3.1 Hydroxyanthracene derivatives (HADs) are a class of phenolic, anthranoid compounds found in various botanical families and genera. Most notably these are plants from the genera Rheum which includes rhubarb; Cassia which includes senna, Indian laburnum and cinnamon; Rhamnus which includes buckthorn; and Aloe which includes aloe vera and bitter aloe. Many of the active compounds under discussion will occur in plants from more than one genus.

3.2 In 2013, the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) published an assessment of the health claims related to the use of HADs in food for the improvement of bowel function (EFSA, 2013). The Panel established a cause- and-effect relationship for this effect (that is, stimulation of colonic motility, which reduces fluid absorption from faecal mass, leading to short-term alleviation of constipation). The Panel considered that in order to obtain the beneficial effect, a product should provide 10mg HADs/day in the adult population.

3.3 In 2018, at the request of the European Commission, EFSA published a scientific opinion on the safety of HADs for use in food, namely emodin, aloe-emodin, danthron, and their preparations. In this opinion, the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded that HADs should be considered as genotoxic and carcinogenic unless there is specific data to the contrary, and that there is a safety concern for extracts containing HADs, although uncertainty persists. The ANS Panel was unable to provide advice on a daily intake of HADs that does not give rise to health concerns. Subsequently, the European Commission proposed restrictions on food supplements that are prepared from Aloe species as they contain HADs.

3.4 Representatives of the food supplements industry noted that the restrictions also apply to preparations of Aloe species where the level of HADs has been removed as far as is technically possible. An additional industry concern was that some Aloe species products contain lower levels of HADs compared to those products that were assessed by EFSA. Overall, industry representatives consider that other risk mitigation measures (such as setting a maximum level for HADs, imposing labelling requirements, and collecting additional safety data) would

allow EFSA to refine its assessment on the health risk posed by Aloe preparations.

3.5 The Nutrition Labelling Composition and Standards (NLCS) policy group has been set up under the NLCS provisional common framework, to maintain a consistent and co-ordinated policy approach across the UK (DHSC, 2020). The NLCS framework sets out arrangements for co-operation between officials in DHSC, Food Standards Scotland (FSS) (representing Scottish Government), Welsh Government (WG) and the Food Standards Agency Northern Ireland (FSANI) with regard to NLCS policy.

3.6 All future policy proposals relating to nutrition are considered on a 4-nation basis via the NLCS policy group, with the impact assessed on the UK as a whole not just each individual nation or Great Britain (GB). The risk assessment and risk management processes of amendments to legislation (including food supplements) in scope of the provisional NLCS framework includes seeking scientific evaluation from the relevant scientific advisory committee, where appropriate.

3.7 On the request of the NLCS policy group, the UK FSA commissioned an independent view from the Committee on Mutagenicity (COM) to advise on the genotoxicity of HADs based on the 2018 EFSA opinion and any new data that has become available since that was published.

3.8 Following the evaluation by the Committee on Mutagenicity (COM), it was taken for review to the Committee on Carcinogenicity (COC) for their opinion on the carcinogenic potential of HADs.

3.9 The FSA had requested that the COC review relevant carcinogenicity studies, evaluate the risk of the HADs and whether a health-based guidance can be derived from the available information.

3.10 The NLCS policy group will assess whether or not to restrict food products containing HADs in GB, considering the conclusions of the COM and COC.

Summary of the Genetic Toxicity Evaluation by COM

3.11 In September 2021, a summary of the EFSA ANS opinion (2018) and additional literature review of relevant publications since the 2018 EFSA opinion was presented to the COM for its consideration on the genotoxic potential of HADs (COM, 2021).

3.12 The COM agreed at the September 2021 meeting, that, overall, the available evidence, namely from Ames tests, indicates that emodin, aloe-emodin, and danthron are genotoxic in vitro. Where mixed results for in vitro genotoxicity have been reported in the literature, this is sometimes due to a lack of clarity on the preparation used for testing: decolourised extracts (which are generally negative as they contain a far lower concentration of HADs), and whole extract (which are positive as they contain greater concentrations of HADs). However, more information is needed to be confident that there was also genotoxicity in the mammalian cell assays, because the mouse lymphoma and micronucleus data that is summarised by the EFSA opinion were published in 1996 (since then, changes have been made to how genotoxicity is evaluated, for example to make sure excessive doses are not used), and also because Müller et al. (1996) did not perform statistical evaluation of the data. Therefore, overall, it was not clear to the COM if the positive results in the mammalian cell assays are indeed positive, or rather, reflective of excessively high concentrations. In terms of in vivo genotoxicity, there was a question as to how much weight should be placed on negative mouse data published after 2018, as EFSA agreed that mice appear to be less sensitive than rats to the gastrointestinal effects caused by HADs. The COM agreed that the studies published after 2018 are mostly negative in vivo data, which weaken the evidence that there is a genotoxic effect in vivo.

3.13 The COM considered that the genotoxic effects of HADs, including those seen in the comet assay of colon cells, are caused by the high levels of irritation, inflammation, and diarrhoea. The 2-fold increase in tail moment (present at all dose levels) in colon cells under the comet assay was not caused by DNA reactivity, but rather an indirect mechanism involving ROS generation and/or topoisomerase II inhibition (mechanisms that were indicated from in vitro data).

Summary of the Carcinogenicity Evaluation by COC

3.14 Following the evaluation by the COM, in March 2022 a discussion paper on the safety of HADs for use in food was brought to review by the COC for its opinion on the carcinogenic potential of HADs (COC, 2022). The FSA requested that the COC review the carcinogenicity studies provided in the paper and evaluate the risk of HADs and whether a health-based guidance value (HBGV) could be derived from the information.

3.15 The COC determined that there were currently insufficient data from the shorter-term studies available to inform an assessment and conclude whether or not there was a safety concern for plant extracts containing HADs. Additionally, the COC established that it would not be possible to set a HBGV for HADs as a single group as they are complex mixtures of different compounds with different mechanisms of action.

3.16 Following a call to industry for new information and data, CRN UK were able to provide the FSA with a record of relevant journal articles that had not been considered in the original EFSA opinion. Following an assessment of the information provided, the Secretariat had determined that one of the articles was able to address some of the questions raised by the Committee at the March 2022 meeting.

3.17 In July 2022 an additional article was presented to the Committee, the article suggested a potential HBGV for HADs. Members determined, as this HBGV was not based upon any new data, that the value presented was based upon many different variables including different strains of animals used, different dosing regimens and varied endpoints analysed. The Committee decided that, at present, there were insufficient data to conclude on an appropriate HBGV for HADs.

3.18 The Annex to the statement presents consumption levels of HADs for a variety of foodstuffs for which there is data and a subsequent exposure analysis. Based on the single value presented for combined exposure for food, aloe drinks and cosmetics the exposure to humans is probably less than would be expected to cause adverse health effects in humans. However, there are large knowledge gaps that would need to be addressed in order to conclude on the safety in humans.

3.19 Future work would have to address that HADs are a diverse group of compounds. Therefore, each compound would need to be analysed and assessed in their own right according to their mechanisms of action and individual levels of exposure from the diet, and cosmetics. There is likely to be a great degree of variation between different HAD compounds. The data presented in Annexe A does not represent an exhaustive list of commodities that contain HADs and are therefore likely to be an underestimation of their consumption in the diet. More information on the level of individual HADs in a wider spectrum of foodstuffs would be required for a full exposure assessment. In addition to food, aloe drinks and cosmetics, exposure from supplements should also be included in a full exposure assessment. Currently, data for supplements is not available.

3.20 Due to insufficient UK data, the COC was unable to make recommendations on a HBGV for HADs, individually or together. Should sufficient data on the toxicity and UK exposure of individual HADs become available, it may then be possible to undertake full and specific risk assessments.

3.21 The interim position can be found here: Interim position on the safety of hydroxyanthracene derivatives for use in food - GOV.UK.