Public consultation - European Parliament and of the Council as regards botanical species containing hydroxyanthracene derivatives (HAD)

General comments

The Council for Responsible Nutrition (CRN), the leading trade association that represents dietary/food supplement and functional food manufacturers and their nutritional ingredient suppliers in the United States, appreciates the opportunity to provide input on amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards botanical species containing hydroxyanthracene derivatives (HAD).

Since founding in 1973, CRN and its members are committed to manufacturing and marketing products for public health and has consistently advocated for (1) a responsible and safe use of dietary/food supplements, functional foods and their nutritional ingredients based on the totality of the scientific evidence and (2) regulations to be proportionate to the risk identified. While CRN appreciates the work EC is taking on to also protect public health, we have serious concerns over the proposed regulation, which intends to prohibit all *Aloe* spp. containing HADs without specifying any threshold level to exclude safe products. The proposed regulation does not take into proper account the totality of scientific evidence on the safety of certain preparations of *Aloe vera,* particularly decolorized (aka, purified) *Aloe vera* whole leaf extract or juice with *de minimis* HAD. Without a comprehensive review of the scientific evidence, the regulation will not be proportionate. For these reasons, CRN opposes the proposed regulation on the blanket ban of *Aloe* spp. containing HADs.

CRN wishes to outline our review of (1) scientific evidence on safety of decolorized *Aloe vera* whole leaf extract with *de minimis* HAD, (2) the regulatory permissibility within the United States of food and dietary supplement products containing decolorized *Aloe vera* whole leaf extract prepared with *de minimis* HAD, and (3) the potential unintended consequences on common foods in European diet.

(1) Scientific evidence on the safety of decolorized *Aloe vera* whole leaf extract with *de minimis* HAD

In reviewing the European Food Safety Authority's (EFSA) 2018 scientific opinion, we found that the panel did not include a thorough review of all existing scientific evidence available on decolorized *Aloe vera* whole leaf extract.[1] The only study EFSA included was an *in vitro* study[2] using test material that was claimed to be a "decolorized aloe whole leaf extract (WLD)" when in fact the material had significantly higher levels of HADs (aloin of 63 mg/kg) compared to the ingredient the industry is using (10 mg/kg), following the International Aloe Science Council's industry standard. Contrary to this *in vitro* study results showing mutagenicity in WLD (aloin of

[1] ANS Panel (2018) Scientific Opinion on the safety of hydroxyanthracene derivatives for use in food. EFSA Journal 16(1):5090, 1-97.

[2] Guo, X., et al., *In vitro* investigation of the mutagenic potential of *Aloe vera* extracts. Toxicol Res-UK, 2014. 3(6), 487-496.

63 mg/kg), a recent study (Hu et al., 2019) using the same mouse lymphoma assay on decolorized *Aloe vera* whole leaf extract with *de minimis* HAD (aloin of 0.3 mg/kg) revealed that this material is not genotoxic.[3] Also, several toxicological studies demonstrating no adverse effects of decolorized *Aloe vera* whole leaf extract and gel with *de minimis* HAD are available, but EFSA did not include in their assessment as relevant data.[4,5,6] Another important study (Shao et al., 2013) that was not reviewed by EFSA is a 13-week toxicology study conducted on decolorized *Aloe vera* whole leaf extract with *de minimis* HAD (<0.1 mg/kg), which showed that the test material did not cause development of precancerous lesions in the colon of the rats.[7] After reviewing these studies, the International Agency for Research on Cancer (IARC) drew a conclusion in its assessment of *Aloe vera* in 2016 and did not classify purified (decolorized) *Aloe vera* whole leaf extract as a carcinogen.[8] As such, we urge the European Commission to take the totality of scientific evidence in to consideration before implementing an overly broad prohibition of *Aloe* spp. in foods and food supplements.

(2) Decolorized *Aloe vera* whole leaf extract with *de minimis* HAD are acceptable ingredients in the U.S.

U.S. food regulations require an attestation of "no harm" to a *reasonable certainty standard*[9], which in the eyes of the U.S. FDA have been met for food products that contain decolorized *Aloe vera* whole leaf and inner leaf products. For dietary supplements, the U.S. regulations require a *reasonable expectation*[10] of no harm would be observed when the dietary supplement is consumed per label directions.

To date, and in accordance with all of the published safety data available for purified *Aloe vera* leaf juice prepared with *de minimis* HAD, the U.S. FDA has not found scientific cause to deem the use of this ingredient in either food or dietary supplement products unsafe, that is, the

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[3] Hu et al. (2019) Absence of mutagenic and clastogenic effects of decolorized *Aloe vera* whole leaf juice concentrate in mammalian cells by the L5178Y/TK+/- mouse lymphoma assay. Toxicol Lett, 314(S1), S301.

[4] Williams et al. (2010) Safety studies conducted on a proprietary high-purity *Aloe vera* inner leaf fillet preparation, Qmatrix. Regul Toxicol Pharm, 57(1), 90-98.

[5] Sehgal et al. (2013) An *in vitro* and *in vivo* toxicologic evaluation of a stabilized *Aloe vera* gel supplement drink in mice. Food Chem Toxicol, 55, 363-370.

[6] Sehgal et al. (2013) Toxicologic assessment of a commercial decolorized whole leaf *Aloe vera* juice, lily of the desert filtered whole leaf juice with aloesorb. J Toxicol, 802453.

[7] Shao et al. (2013) Safety of purified decolorized (low anthraquinone) whole leaf *Aloe vera* (L) Burm. F. juice in a 3-month drinking water toxicity study in F344 rats. Food Cjhem Toxicol. 57, 21-31.

[8] IARC. (2016) IARC Working Group on the Evaluation of Carcinogenic Risks to Humans - Monograph for *Aloe Vera*. IARC monographs on the evaluation of carcinogenic risks to humans. 108. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Drugs-And-Herbal-Products-2015.

[9] TITLE 21--FOOD AND DRUGS; CHAPTER I--FOOD AND DRUG ADMINISTRATION; DEPARTMENT OF HEALTH AND HUMAN SERVICES; SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED); PART 180 -- FOOD ADDITIVES PERMITTED IN FOOD OR IN CONTACT WITH FOOD ON AN INTERIM BASIS PENDING ADDITIONAL STUDY; Subpart A--General Provisions; Sec. 180.1 General; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=180.1.

[10] TITLE 21--FOOD AND DRUGS; CHAPTER I--FOOD AND DRUG ADMINISTRATION; DEPARTMENT OF HEALTH AND HUMAN SERVICES; SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED); PART 190 -- DIETARY SUPPLEMENTS; Subpart B--New Dietary Ingredient Notification; Sec. 190.6 Requirement for premarket notification.; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=190.6.

ingredient is found to be both reasonable expected and reasonable certain to cause no harm in dietary supplement and food products, respectively.

In the U.S. at the federal level, liquid products with decolorized *Aloe vera* whole leaf extract with *de minimis* HAD are regulated by FDA as shelf-stable (non-refrigerated) acidified foods, defined as a "low-acid food with a natural pH of 4.6 or below to which acids or acid foods are added."[11,12] The processors of shelf stable acidified foods must register with FDA as a Food Canning Establishment and provide detailed formula, process and container information.

At the U.S. State level, some States have additional regulations for liquid aloe beverages that are classified as acidified foods. For instance, in California, these products are considered shelf-stable (non-refrigerated) acidified foods. These products must comply with the California Department of Public Health's (CDPH) requirements in addition to the federal requirements. CDPH requires processors for shelf-stable acidified foods to obtain a Cannery License, which must be renewed every two years. In addition to the Cannery License, CDPH requires that each lot of shelf-stable acidified foods only be released into commerce after a CDPH inspector has verified that the pH control and the critical factors, such as microbiology specifications, are met.

By regulating aloe beverage products under the acidified foods at the federal and State level, it is clear that decolorized *Aloe vera* whole leaf extract with *de minimis* HAD is accepted as a safe ingredient for human consumption in the U.S.

(3) <u>The potential unintended consequence on common foods in European diet</u>

We would like to point out that EFSA also did not address the important issue of HAD compounds that are present in commonly consumed vegetables and legumes. Analysis has shown that HAD compounds are found at measurable levels in edible parts of lettuce (5.9 mg/kg), cabbage (3.6 mg/kg), green beans (36 mg/kg), and garden peas (0.04 mg/kg).[13] As these are commonly consumed food, EC should properly evaluate daily exposure of HAD from these items compared to exposure from decolorized *Aloe vera* whole leaf extract with *de minimis* HAD in food and food supplements. We encourage EC to consider potential unintended consequences of a blanket prohibition of *Aloe* spp. containing HAD into the risk management decision.

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[11] TITLE 21--FOOD AND DRUGS; CHAPTER I--FOOD AND DRUG ADMINISTRATION; DEPARTMENT OF HEALTH AND HUMAN SERVICES; SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION; PART 108 -- EMERGENCY PERMIT CONTROL; Subpart B--Specific Requirements and Conditions for Exemption From or Compliance With an Emergency Permit; Sec. 108.25 Acidified foods; https://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=108.25.

[12] TITLE 21--FOOD AND DRUGS; CHAPTER I--FOOD AND DRUG ADMINISTRATION; DEPARTMENT OF HEALTH AND HUMAN SERVICES; SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION; PART 114 ACIDIFIED FOODS; https://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=114.

[13] Mueller et al. (1999) Occurrence of emodin, chrysophanol and physcion in vegetables, herbs and liquors. Genotoxicity and antigenotoxicity of the anthraquinones and of the whole plants. Food Chem Toxicol 37, 481-491.

Conclusion

We respectfully oppose the overly broad prohibition of *Aloe* spp. containing HAD and propose the EC to use more proportionate approach after taking into the consideration all existing scientific evidence for safe aloe products that have a long history of safe use, as well as dietary HAD exposure from other common foodstuffs, which may be higher than the exposure from foods and dietary/food supplements containing decolorized *Aloe vera* whole leaf extract with *de minimis* HAD. We propose the EC to establish a risk-based threshold level and clearly exclude safe products from prohibition.

Respectfully submitted,

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