European Federation of Associations of Health Product Manufacturers

EHPM contribution to the feedback mechanism of proposed Regulation amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards botanical species containing hydroxyanthracene derivatives - Ares (2020)1357432

The European Federation of Associations of Health Product Manufacturers (hereinafter, **EHPM)**, EU stakeholder registered on the EU Transparency Register (No. 65512466920-96) would like to submit its contribution in the context of the consultation on the proposed draft Regulation amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards botanical species containing Hydroxyanthracene Derivatives (Ares (2020)1357432).

The Covid-19 health emergency and the measures implemented by Member States to limit the spread of this virus are causing major difficulties for companies in the food supplement sector, the large part of which are SMEs. The priorities for companies are twofold at the moment. They have to protect their workers (making sure all the necessary measures are in place to guarantee their safety) and at the same time they need to maintain the production in order to satisfy consumers' needs and revenue. Keeping up with the production is extremely difficult due to the significant scarcity of raw materials, while production faces the limitations of physical presence work in factory. Thus, most of the companies are implementing business continuity plans in order to survive. Therefore, we call upon the Commission to pause the consultation for time needed to companies to cope with such an unprecedented emergency. That would allow companies to focus on the measures to contrast the emergency but also to provide a high-quality feedback once this crisis situation regarding Covid-19 will be over. In order to assess the potential impact of the suggested ban of the use of aloe preparations in food supplements, we have conducted a survey among our members. More in specific, we have asked them to indicate the type of product sold, the ingredient used, the purpose of Aloe used and the HADs content as well as to indicate whether a product reformulation with alternatives would be feasible. The highlights of this survey are available in Annex 10.

Considering that most of our members are SMEs that are currently overwhelmed by the Covid-19 outbreak, they were not able to provide all data in such a short notice. However, the results of this exercise show the significant impact of the proposed measure on the food supplement sector. Moreover, we compared our results with those of other organizations that conducted similar surveys and the same trend is confirmed.

With reference to the text of the draft regulation, which proposes to ban

i) aloe-emodin and all extracts in which this substance is present;
ii) emodin and all extracts in which this substance is present; and
iii) extracts from the leaf of *Aloe* species containing hydroxyanthracene derivatives;

we believe that such a blanket ban would be disproportionate taking into account the following elements:

- The established history of use without adverse events being reported;
- The shortcomings of the scientific opinion published by EFSA[1] on which this regulatory proposal is based;
- The essential scientific remarks we mention below;
- The fact that there are more proportionate measures available to achieve the same goal.

We would also like to highlight that the option to place substances under scrutiny, as established in the Implementing Regulation (EU) No 307/2012, imposes unrealistic and restrictive timelines on industry which are difficult to meet considering the type of the studies needed for this type of assessment. Moreover, taking into account that it would be necessary to agree on the appropriate methodology and criteria for the safety assessment, as well as the type of studies to be conducted for this specific type of ingredients it would be important to have a direct dialogue with EFSA. For instance the implementation of the revised General Food Law[2] regulation that foresees the possibility of pre-submission advice between EFSA and the stakeholders could offer such opportunity.

We believe that the main scientific limitations of the EFSA opinion are the following:

- Indications for assumed toxicity are mainly based on *in vitro* studies bearing severe limitations for extrapolations to actual food use. (Annex 1)
- Pre-clinical studies with unrealistic high doses of isolated components with limited or no value for the evaluation of lower levels of botanical preparations with hydroxyanthracene derivatives (hereinafter, **HADs**) used in food products. (Annex 2)
- Unscientifically based extrapolations obtained with specific synthetic components (even including danthron) to natural occurring HADs with different chemical structures in a botanical matrix. (Annex 3)

[1] Safety of hydroxyanthracene derivatives for use in food: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5090
[2] Art. 32 a of the REGULATION (EU) 2019/1381 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 20 June 2019

- Inadequate or no characterization of the extracts containing HADs on which the final opinion was based. (see references in EFSA-opinion and Annex 4)
- Disregard and exclusion of studies indicating that no correlation could be found between use of botanical preparations containing HADs and increased risk for intestinal cancer or other harmful effects. (Annex 5)
- Absence of human studies demonstrating the carcinogenic effects of HADs containing laxatives. (see references in EFSA-opinion)
- Extrapolations of observations found with pure isolated components to plant-based preparations, disregarding the generally accepted and proven matrix effects. (Annex 6)
- Extrapolations from data not relevant for preparations containing HADs. (Annex 7)
- Lack of consideration of the pharmacokinetics of HADs. (Annex 8)
- Disregard of the existence of well-known pleiotropic effects, characteristic for plant-based products generally accepted, also by toxicologists.
- A lack of consideration of all relevant plant species containing HADs, despite the request of the Commission to EFSA[3] to assess all relevant information on the safety use of HADs from all sources in food. For instance, other plants would be *Rumex s*p., *Phaseolus vulgaris* L.and *Lactuca sativa L*. Strict implementation of the criteria set by the opinion will also prohibit the use of lettuce and beans. (Annex 9)

As a consequence, the final opinion of EFSA basically only considers a few, very specific studies showing little value to the practical use of preparations containing HADs. Taken all together, one could pose it lacks a sound scientific basis to confirm that there would be a risk for public health for these traditionally used products.

Considering that products containing HADs have been sold for several decades in all EU Member States and outside the EU without any serious adverse event reported, and even EFSA in its positive opinion on the health claim in 2013[4] indicated as only warning the avoidance of prolonged use, we believe that the origin of the launch of Art. 8 procedure should be found elsewhere. In fact, the summary of the Standing Committee meeting of 5th December 2013,

[3] Mandate letter sent from the EC to EFSA on the 30th of June 2016 ARES (2016) 3067207
[4] Scientific Opinion on the substantiation of a health claim related to hydroxyanthracene derivatives and improvement of bowel function pursuant to Article 13(5) of Regulation (EC) No 1924/2006: https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2013.3412

during which Member States' experts discussed the EFSA Scientific opinion on the health claim related to the hydroxyanthracene derivatives and the improvement of bowel function, suggests that some Member States consider products containing hydroxyanthracene derivatives to be food supplements, while others view them as (herbal) medicines. Thus, it seems that borderline considerations played a key role in the Commission's decision to use the procedure under Article 8 of Regulation (EC) 1925/2006.

Moreover, the EFSA's opinion of 2018 also draws on data, which relates to the use of hydroxyanthracene derivatives in medicinal products, rather than food supplements. However, a borderline determination between medicine and food supplement is outside the scope of EFSA's competence. The competence for the assessment of medicinal products (and not food) lies with the European Medicines Agency (EMA) and national competent authorities in the Member States pursuant Article 55 of Regulation (EC) 726/2004. Nevertheless, recital 2 of the draft Implementing Regulation expressly refers to the use of hydroxyanthracene derivatives in herbal medicinal products. Finally, pursuant to article 8 §2, point (b) of Regulation 1925/2006, substances shall be placed in Annex III, Part C if the possibility of harmful effects is identified but scientific uncertainty persists. On page 5, EFSA concluded that "*there is a safety concern for extracts containing hydroxyanthracene derivatives although uncertainty persists.*". Consequently, in light of these severe limitations of the EFSA opinion:

i) We question if the assessment of this uncertainty could have been executed in line with the principles and methods described in the Guidance on Uncertainty Analysis in Scientific Assessment[5]; and

ii) We infer that, given the scientific uncertainty recognized by the EFSA itself, Regulation 1925/2006 at most permits that substances are placed under scrutiny (Part C), but does not yet warrant their prohibition (Part A).

Furthermore, a ban on aloe-emodin and emodin and all extracts containing them would be in contrast with the decision to place the other plants containing HADs under scrutiny. Even the plants currently placed in Part C of Annex III contain certain, albeit low amounts of aloe-emodin and emodin. Consequently, if they would be prohibited, the ban would encompass also plants currently proposed for scrutiny. HADs are also present in some common vegetables consumed

[5] The principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment. EFSA Journal 2018;16(1):5123, 39 pp. https://doi.org/ 10.2903/j.efsa.2018.5123

daily in a normal diet over a long period. We suppose it is not the intention of the European Commission, or the Member States to prohibit these plants or their preparations inadvertently.

The impact of the measures would be extremely wide given that, on the basis of the studies evaluated, the EFSA was not able to advise on a daily intake of hydroxyanthracene derivatives that would not give rise to concerns about harmful effects to health. So, such blanket ban would affect all foods and drinks containing aloe extracts and any level of the substances proposed to be banned. Such measure would largely exceed what is necessary to achieve the objective.

In light of the above, we believe that the most appropriate, proportionate and logical option at this point would be to move 'aloe-emodin and all extracts in which this substance is present'; 'emodin and all extracts in which this substance is present'; 'extracts from the leaf of Aloe species containing hydroxyanthracene derivatives' to part C of Annex III of the Regulation 1925/2006 as well.

This also would allow for all stakeholders, currently under extreme financial stress, to provide the necessary additional information about the safety of their products and for the European Commission and the Member States to consider proportionate risk management measures that would guarantee a balanced approach safeguarding consumers' health. For instance, with mandatory warnings against the prolonged use as suggested by EFSA in its 2013 opinion. We really hope that the Commission will take our contribution into account. We are available for further explanation or discussion of the elements summarized in our contribution.

About the EHPM: EHPM was created in 1975 and represents 1600 health-product manufacturers in 14 European countries. Through our member associations EHPM aims to provide consumers with safe, science-based, high quality products as well as accurate and helpful information about their nutritional value and use and to assure a fair European regulatory framework for our sector.

Annex 1: Limited value of *in vitro* data

In vitro mutagenic effects were reported for emodin and aloe-emodin. However, several of them **could not be confirmed *in vivo*** (1-3).

1. **Heidemann A. et al**, 1993. The genotoxicity status of *Senna*. Pharmacology 47 (suppl.1): 178-186.
2. **Heidemann A. et al**, 1996. Genotoxicity of Aloe-emodin in vitro and in vivo. Mutat. Res. 367:123-133.
3. **Mueller SO et a**l, 1998. Biotransformation of the Anthraquinones Emodin and Chrysophanol by Cytochrome P450 enzymes. Drug Metabolism and Disposition 26 (6): 540-546.

Annex 2: Unrealistic approach of pre-clinical studies

In those cases where an *in vivo* toxicity was reported, this was only noticed when administering high to **very high amounts of pure components and/or during very long periods** considering the average life time of the test animals (1-2). Comparable doses are not encountered when considering practical applications where much lower amounts are applied.

When considering doses applied in the 2001 NTP-study (3) on the toxicity study of emodin and conversion of these doses administered to animals to human use, according to the FDA algorithm, **values between 200 and 24000 mg/day** are found for middle long time application (16 days - 14 weeks) **and 70 and 10.800 mg/day** for very long time application (2 years). This can hardly be considered as a realistic approach for food products.

1. **Jahnke GD et a**l. 2004. Developmental Toxicity Evaluation of Emodin in Rats and Mice. Birth Defects Research 71:89-101.
2. **Xiaoxv D. et al**. 2016. Emodin: A Review of its Pharmacology, Toxicity and Pharmacokinetics. Phytother. Res. 30: 1207-1218
3. **Natl. Toxicol Program** Tech Rep. Ser. 2001. Toxicology and Carcinogenesis Studies of EMODIN (CAS NO. 518-82-1) Feed Studies in F344/N Rats and B6C3F1 Mice 493: 1-278

Annex 3: unreliability of data on synthetic components

Comparing the carcinogenic activities of representatives of amino, alkyl, nitro, hydroxyl, or halogen-containing anthraquinones which were administered to Fischer 344/N rats and B6C3F mice, revealed that, while anthraquinone and the amino- and nitro-derivatives were highly tumorigenic, there was **no evidence of carcinogenic activity of the hydroxyl-anthranoid emodin** in male rats and female mice. (1)

When investigating the effects of synthetic anthraquinones, it was demonstrated that some of the **products tested were contaminated with mutagenic compounds**, particularly 9-

nitroanthracene, resulting in confounding reports about the genotoxic potential of anthraquinones. (2-3)

A special remark has to be made towards the conclusions in the EFSA-document based on effects obtained **with danthron.** One needs to pose the question why toxic effects were found with this component and why was it used as a reference in this evaluation. Toxicity of danthron has been proven and is generally accepted. However, it is a synthetic component and has **never been found in the plants species *Senna*, *Rheum*, *Aloe* or *Frangula***. The essential difference between danthron and the naturally occurring hydroxyanthracenes in the genera mentioned above is the absence of a substitution in the 3- and 6-position. **This is essential and fundamental when comparing toxicity profiles**.

The toxicity of benzene has been clearly demonstrated while benzoic acid is generally accepted as food additive. The only difference is a carboxyl group present in benzoic acid and absent in benzene. Similarly, the absence of danthron in the products in question has to be taken into account. Consequently, it is questionable that the toxicity profile of danthron is extrapolated to all hydroxyanthracenes and used to justify the potential danger of plant-based products containing them. **Lumping together a complex group of chemical components has never been proven the right scientific approach when considering specific properties and certainly not when investigating toxicity.**

1. **Doi AM et al**. 2005. Influence of functional group substitutions on the carcinogenicity of anthraquinone in rats and mice: Analysis of long-term bioassays by the National Cancer Institute and the National Toxicology Program. J. Toxicol. Environ. Health B Crit. Rev. 8(2): 109-126.
2. **Butterworth BE et al.** 2001. The preparation of anthraquinone used in the National Toxicology program cancer bioassay was contaminated with the Mutagen 9-nitroanthracene. Mutagenesis 16: 169-177.
3. **Buterworth BE et al**. 2004. Contamination is a frequent confounding factor in toxicology studies with anthraquinone and related compounds. Int. J.Toxicol. 23: 335-344.

Annex 4: inadequate characterization of extracts

In one of the studies used in order to prove the toxicity of *Aloe*-extracts (1), a gamma-irradiated whole leaf extract was investigated. However, no information is available on the effects on

chemical composition resulting from the irradiation. Moreover, the **potential influence of irradiation on the results observed is even not considered**.

1. **Natl. Toxicol Program**. 2013. Toxicology and carcinogenesis studies of a nondecolorized whole leaf extract of *Aloe barbadensis* Miller (Aloe vera) in F344/N rats and B6C3F1 mice. No 13/5910.

Annex 5: exclusion of studies questioning the harmful effects

Striking different observations as those reported above (Annex 4) were reported in two chronic toxicity studies (1 and 2 years) carried out on a non-decolorized *Aloe* leaf extract were no gamma irradiation was applied. (1-2) These studies were conducted on an animal model similar to and having the same duration as the NTP, 2013 study. (Annex 4)

In these studies, a **NOAEL** (Non observable adverse effect level) was found for the non-decolorized *Aloe* whole leaf extract reaching 0.16 % of the weight of the diet of the animals, **corresponding to 87.7 and 109.7 mg/kg/day** for male and female rats, respectively.

When considering the collection of experiments related to the potential effect of *Senna* and sennosides, Morales et. al. concluded the following: “There is **no relation between long term administration of a senna extract and the appearance of gastrointestinal tumors or any other type** in rats (Even after a two-year daily dose up to 300 mg/kg/day). Moreover, they stated that “the current evidence **does not show** that there is **a genotoxic risk** for patients who take laxatives containing senna extracts or sennosides. There is no convincing evidence that the chronic use of senna has, as a consequence, a structural and/or functional alteration of the enteric nerves or the smooth intestinal muscle”. (3)

Several experimental designs have been used to study possible cancerogenic risks of anthranoids in humans. (4-16) Most of these studies do not support the relationship between the use of anthranoids and colorectal cancer. The few reports were a relation was reported between use of anthranoids and changes noticed in colon anatomy that may point to an increased risk for developing colon cancer were all related to the use of **massive doses in combinations with other components** and/or long term use (up to 5 years). Also, the relation observed between the occurrence of *Pseudomelanosis coli* and colorectal adenomas could be explained by the easier detection of the tiny polyps appearing as white spots within the background of dark-colored mucosa.

A meta-analysis on constipation and cathartics as risk factors for colorectal cancer found a small but significant risk. (17) The authors showed that this risk rather reflected a **confounding influence on dietary** habits. Therefore, the question can be raised as to whether the increased risk reported in some studies should not be related to changes in unknown aetiology or to the constipation itself as a constitutional factor. This was confirmed by the results from a case-control study where a positive association was found between constipation and colon carcinoma. There was no association with laxative use. (18)

1. **Matsuda Y. 2008.** One-year chronic toxicity study of *Aloe arborescens* Miller var. *natalensis* Berger in Wistar Hannover rats. A pilot study. Food Chem Toxicol., 46(2), 733-739.
2. **Yokohira M. 2009**. Equivocal colonic carcinogenicity of *Aloe arborescens* Miller var. *natalensis* Berger at high-dose level in a Wistar Hannover rat 2-y study. J. Food Sci, 2009, 74: T24–T30.
3. **Morales et al. 2009**. Is Senna laxative use associated to cathartic colon, genotoxicity, or carcinogenicity? Journal of Toxicology 2009: 1-8.
4. **Siegers CP et al. 1993.** Anthranoid-laxative abuse – A risk for colorectal cancer? Gut 34 (8):1099 – 1101.
5. **Kune GA et al. 1988.** The role of chronic constipation, diarrhea and laxative use in the etiology of large-bowel cancer. Data from the Melbourne cancer study. Diseases of the colon and rectum 31: 507-512.
6. **Kune GA 1993.** Laxative use is not a risk for colorectal cancer: Data from the Melbourne Colorectal Cancer Study. Z. Gastroenterol. 31: 140 – 143.
7. **Riecken EO et al. 1990.** The effect of an anthraquinone laxative on colonic nerve tissue: a controlled trial in constipated women. Z. Gastroenterol. 28: 660 – 664.
8. **Nusko G et al. 1993.** Retrospective study on laxative use and Melanosis coli as risk factors for colorectal neoplasma. Pharmacology 47 (suppl. 1): 234 - 241.
9. **Nusko G et al. 1997.** Melanosis coli: A harmless pigmentation or a precancerous condition? Z. Gastroenterol. 1997; 35 (5): 313-318.
10. **Nusko G et al. 2000.** Anthranoid laxative use is not a risk factor for colorectal neoplasia: Results of a prospective case control study. Gut 46 (5): 651 – 655.
11. **Loew D et al. 1994.** Anthranoid laxatives: cause of colorectal cancer? Deutsche Apotheker-Zeitung 134 (30): 30-33.

12. **Jacobs EJ and White E, 1998.** Constipation, laxative use, and colon cancer among middle-aged adults. Epidemiology 9(4): 385 – 391.
13. **Joo J et al. 1998.** Alterations in colonic anatomy induced by chronic stimulant laxatives. The Cathartic Colon Revisited. J. Clin. Gastroenterol. 26 (4): 283-286.
14. **Van Gorkom BA et al. 2000.** Influence of a highly purified senna extract on colonic epithelium. Digestion 61 (2): 113-120.
15. **Willems M et al. 2003.** Anthranoid self-medication causing rapid development of Pseudomelanosis coli. The Nederlands Journal of Medicine. 61(1): 22-24.
16. **Ewing CA et al. 2004**. Melanosis coli involving pericolonic lymph nodes associated with the herbal laxative Swiss Kriss: a rare and incidental finding in a patient with colonic adenocarcinoma. Archives of Pathology and Laboratory Medicine 128:565-567.
17. **Sonnenberg A and Müller AD, 1993**. Constipation and cathartics as risk factors of colorectal cancer: a Meta-analysis. Pharmacology 47 Suppl.1: 224-233.
18. **Roberts MC et al, 2003**. Constipation, laxative use, and colon cancer in a North Carolina population. Am. J. Gastroenterol. 98: 857-864.

Annex 6: non-consideration of matrix effects

Mueller et al. found that though pure emodin showed to be genotoxic in mouse lymphoma cells **not any effect could be found in the micronucleus test with a complete, anthraquinone containing, vegetable extract**. Furthermore, an anthraquinone containing lettuce extract completely abolished the induction of micronuclei by danthron, known to be genotoxic on itself. (1) This very clearly indicates a protective effect of the food matrix and again demonstrates that observations made with pure components can not directly be extrapolated to plant preparations.

1. **Mueller SO et al.** 1999. Occurrence of emodin, chrysophanol and physcion in vegetables, herbs and liquors. Genotoxicity ant antigenotoxicity of anthraquinones and of the whole plants. Food Chem. Toxicol. 37(5): 481-491.

Annex 7: consideration of data non-relevant to HADs

In two studies cited by the Panel (1-2), a correlation between chronic use of non-fiber laxatives and the incidence of colon-rectum cancer was reported. These studies, however, **do not specifically report on anthraquinone containing laxatives**. The fact that these observations cannot simply be extrapolated to HADs containing preparations is supported by several other

studies where **no evidence for any correlation between the use of anthraquinone laxatives and increased in incidence on colon-rectum cancer** was found (3-4, see also Annex 5). It was also postulated that damages found to the nervous system in the colon found in some studies may be due to pre-existing changes of the unknown aetiology or to the constipation itself. (5)

1. **Watanabe T. et al.** 2004. Constipation laxative use and risk of colorectal cancer, the Myagi Cohort study. Eur J of Cancer 40: 2109-2115
2. **Cintronberg J. et al.** 2014. A prospective study of bowel movement frequency, constipation and laxative use in colorectal risk cancer. Am J of Gastroenterol 109 (10): 1640-1649.
3. **Nusko G. et al.** 2000. Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective control case study, Gut 46: 651-655.
4. **Nusko, G et al.** 1993. A retrospective study on laxative use and melanosis coli as risk factor for colorectalneoplasma, Pharmacology 47(1): 234-241.
5. **Müller-Lissner SA** et al. 2005. Myths and misconceptions about chronic constipation. Am. J. Gastroenterol. 100(1): 232-242.

Annex 8: non-consideration of pharmacokinetics

In a more recent review the pharmacology and toxicity of emodin is also discussed.(1) Based on *in vivo* tests, kidney and liver were shown to be the main toxic target organs. Again, toxicity was only encountered when applying high doses to the test animals. However, **bioavailability of this compound is very low** (2-4). Combined with a fast phase II-glucuronidation these effects are not to be expected when administrating normal recommended doses of plant-based preparations.

1. **Xiaoxv D. et al.** 2016. Emodin: A review of its pharmacology, toxicity and pharmacokinetics. Phytother. Res. 30: 1207-1218.
2. **Liang JW et al.** 1995. Emodin pharmacokinetics in rabbits. Planta Medica 61(5): 406-408.
3. **Wei Liu et al.** 2012. Coupling of UDP-glucuronosyltransferases and multidrug resistance-associated proteins is responsible for the intestinal disposition and poor bioavailability of emodin. Toxicol. Appl. Pharmacol. 265(3):316-324.
4. **Xiaoxv et al.** 2016. Emodin: a review of its pharmacology, toxicity and pharmacokinetics: emodin: pharmacology, toxicity and pharmacokinetics. Phytother. Res. 30(8): 1207-1218.

Annex 9: exclusion of other HADs-containing plants

The presence of HADs in several plant species not mentioned in the EFSA-opinion is well described in literature (1-4). As non-rhein HADs are also found in lettuce (5.9 mg/kg) and beans (36 mg/kg) also in considerable amounts (1) these vegetables have to be prohibited when accepting EFSA's general opinion.

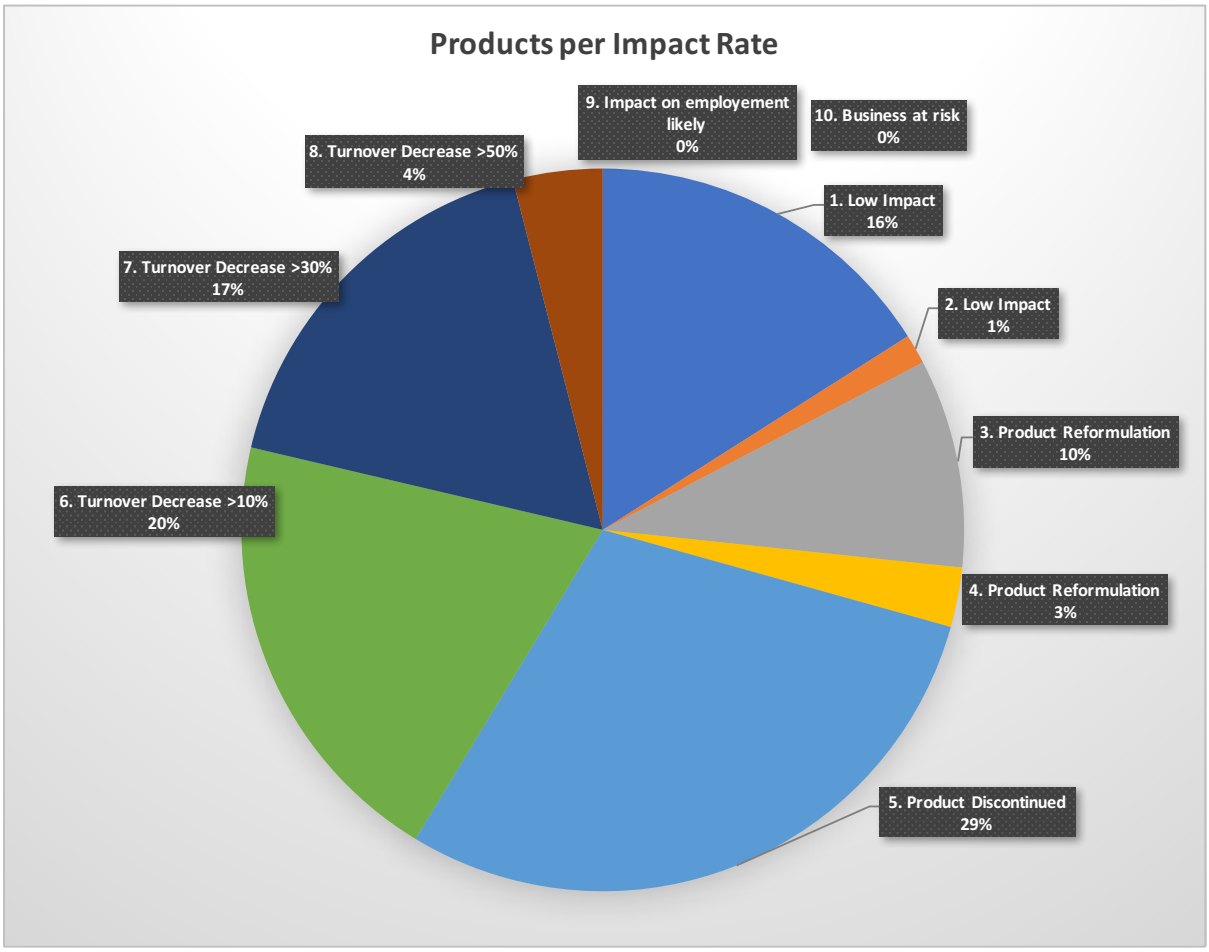
1. **Xiaoxv et al.** 2016. Emodin: a review of its pharmacology, toxicity and pharmacokinetics: Emodin: pharmacology, toxicity and pharmacokinetics. Phytother. Res. 30(8): 1207-1218.
2. **Lonfei L. et al.** 2015. Traditional usages, botany, phytochemistry, pharmacology and toxicology of Polygonum multiflorum Thunb.: A Review. J. Ethnopharmacol. 159: 158-183.
3. **Vasas A. et al.** 2015. The genus Rumex: review of traditional uses, phytochemistry and pharmacology. J. Ethnopharmacol. 175: 198-228.
4. **Mueller SO et al.** 1999. Occurrence of emodin, chrysophanol and physcion in vegetables, herbs and liquors. Genotoxicity ant antigenotoxicity of anthraquinones and of the whole plants. Food Chem. Toxicol. 37(5): 481-491.

Annex 10: highlights of the EHPM survey on the impact of the proposed ban of Aloe preparations in the food supplement sector.

Considering that most of our members are SMEs that are currently overwhelmed by the Covid-19 outbreak, they were not able to provide all data in such a short notice. However, the results of this exercise show the significant impact of the proposed measure on the food supplement sector. Moreover, we compared our results with those of other organizations that conducted similar surveys and the same trend is confirmed. In this unprecedented context, companies are confronted with the most dramatic measures: the ban of products that they have been selling for decades recording no history of adverse events.

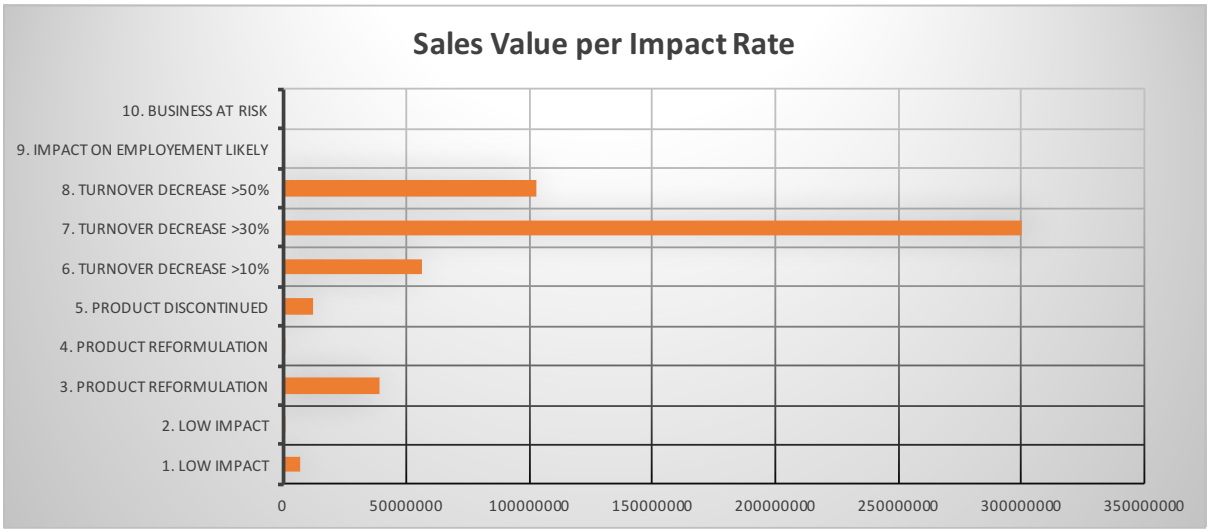
The impact was rated on a scale of 10. The data received concerns 75 impacted products shows:

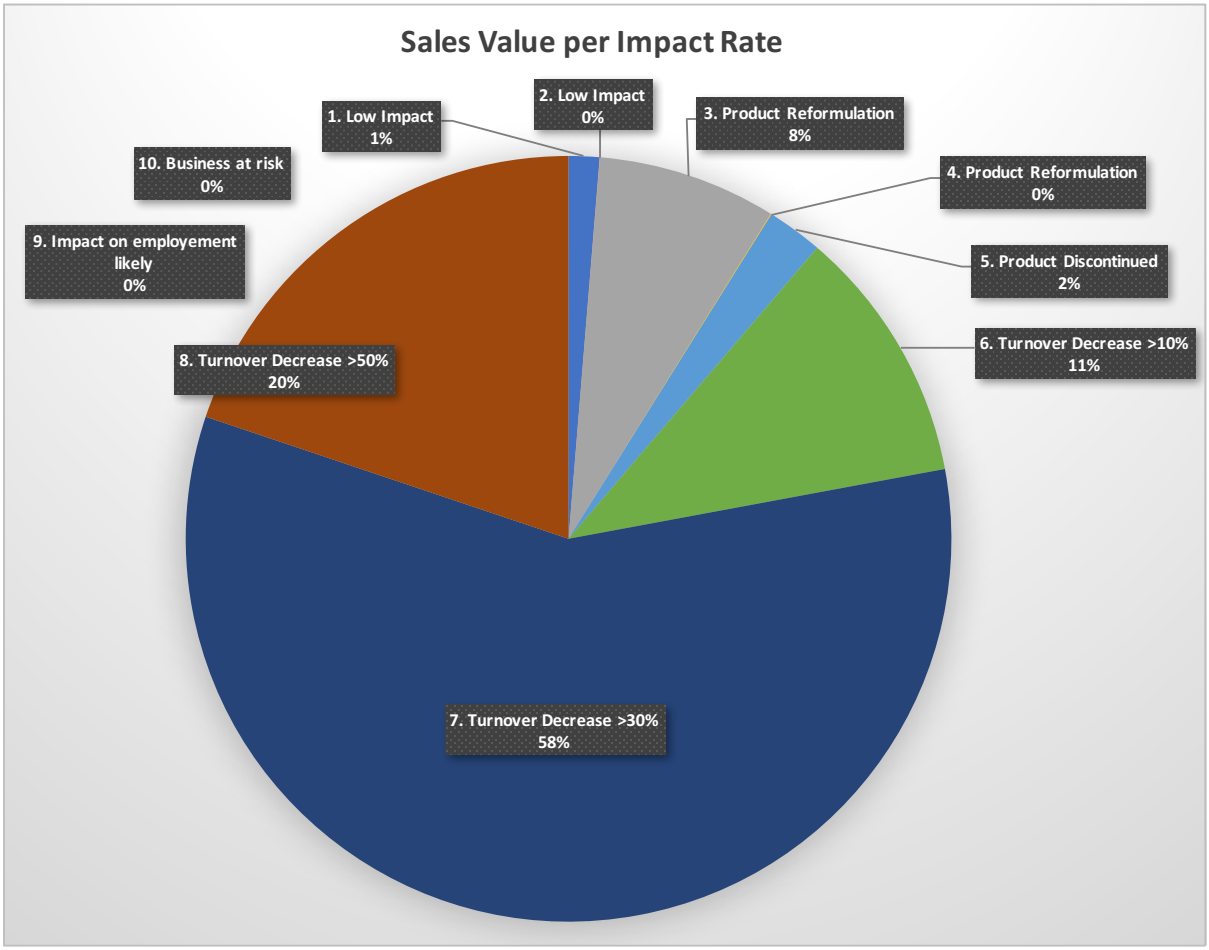
- 17% of the impacted products will have a low impact (1,2)
- 13% of the impacted products will require reformulation (3,4)
- 29% of the impacted products will have to be discontinued (5)
- 41% of the impacted products will negatively affect the whole company turnover (6,7,8)
    - 20% the turnover will decrease with more than 10% (6)
    - 17% the turnover will decrease with more than 30% (7)
    - 4% the turnover will decrease with more than 50% (8)



The data also shows that the sales value of the reported impacted products accounts for over half a billion euro, of which the largest part (89% = EUR 459 022 949) is from impacted products that will negatively affect the company turnover:

- EUR 55 993 175 (11%) is the sales value of the impacted products that will affect the company turnover with more that 10% (6)
- EUR 300 440 760 (58%) is the sales value of the impacted products that will affect the company turnover with more that 30% (7)
- EUR 102 589 014 (20%) is the sales value of the impacted products that will affect the company turnover with more that 50% (8)





We also asked our companies whether a product reformulation with alternatives would be feasible:

- 55% of respondents said that reformulation is not possible as Aloe is the main or only ingredient of the product
- 9% of the respondents said that reformulation would be difficult
- 20% of the respondents said that reformulation would be possible but that would imply the loss of the specific characteristics of the plant
- 9% of the respondents said that reformulation is possible
- 7% of the respondents said that they do not know yet

Significantly, a large part of companies reported concerns that even if the product was reformulated with the use of other plants, these plants could undergo a ban in few years' time if the approach EFSA's applies to the safety assessment of botanicals will remain unchanged.