



General approach to assess the safety for the target species of botanical preparations which contain compounds that are genotoxic and/or carcinogenic when used as feed additives

Endorsed by the FEEDAP Panel during the 153rd Plenary meeting of 17-18 March 2021¹

In the framework of the assessment of feed additives under Regulation (EC) No 1831/2003,² the European Commission requested EFSA to undertake a risk assessment of feed additives of botanical origin. Among these botanical preparations, the FEEDAP Panel has identified some additives which naturally contain substances that are genotoxic and/or carcinogenic.

The EFSA Scientific Committee indicated repeatedly that “substances which are both genotoxic and carcinogenic should not be approved for deliberate addition to foods or for use earlier in the food chain, if they leave residues which are both genotoxic and carcinogenic in food” (EFSA, 2005; EFSA SC, 2012).

Since these substances are naturally present in plants, their presence in low concentrations in botanical preparations intended for use as feed additives cannot be fully avoided and therefore has to be addressed in the assessment of the safety of the target animals, the consumer and the user. In any case, manufacturing processes of botanical feed additives should avoid selective extraction and enrichment of genotoxic and/or carcinogenic substances and should aim at the reduction of these substances. The Guidance on Safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements” (EFSA SC, 2009) states that “In cases ...where the botanical ingredient contains substances that are both genotoxic and carcinogenic, the “Margin of Exposure” (MOE) approach (EFSA, 2005) could be applied covering the botanical(s) under examination and any other dietary sources of exposure. The MOE approach compares toxic effect levels with human exposure levels. Alternatively, it could be evaluated whether the expected exposure to the genotoxic and carcinogenic ingredient is likely to be increased, compared to the intake from other sources.”

Considering the above and in order to address the request of the European Commission, the FEEDAP Panel decided to extend the methodology based on the MOE approach developed by EFSA for human risk assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed (e.g. unavoidable contaminants or by-products resulting from a production, process) to animal risk assessment of botanical preparations intended for use as feed additives (EFSA SC, 2019a).³

The methodology applied to the assessment of the **safety for the target species** of botanical preparations containing substances that are both genotoxic and/or carcinogenic depends on the available dataset on carcinogenicity studies in rodents. Three scenarios are considered possible:

- (i) for substances for which carcinogenicity studies in rodents are available, from which a BMDL₁₀ can be derived, the MOE approach (EFSA, 2005; EFSA SC, 2012) can be applied. Similarly to human risk assessment, a combined (total) margin of exposure (MOET) with a

¹ <https://www.efsa.europa.eu/en/events/event/153rd-plenary-meeting-feedap-panel>

² Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29

³ The proposed methodology was discussed in EFSA Scientific Committee in November 2020 and endorsed for further work strategy by the FEEDAP Panel <https://www.efsa.europa.eu/sites/default/files/event/2020/101st-plenary-meeting-scientific-committee-minutes.pdf>

magnitude of $\geq 10,000$, when comparing estimated exposure to genotoxic and/or carcinogenic substances with a BMDL₁₀ from a rodent carcinogenicity study, would be indicative of a low concern for the target species (EFSA SC, 2019a)

- (ii) when carcinogenicity studies in rodents are not available or would not allow the identification of a reference point to be used in the risk assessment, the threshold of toxicological concern (TTC) concept for genotoxic substances can be applied. Similarly to human risk assessment, for substances that have the potential to be DNA-reactive mutagens and/or carcinogens based on the weight of evidence, (combined) estimated exposures below the TTC value of 0.0025 µg/kg bw per day would be indicative of low probability of adverse effects (EFSA SC, 2019b)
- (iii) when carcinogenicity studies are not available, it could be evaluated whether the exposure to these substances of concern is likely to be increased by the use of the feed additive compared to the intake from other dietary sources. For those animal species that are fed relevant plant materials as part of daily feed, a minimal increase⁴ of the intake of these substances via the feed use of the additive of botanical origin would be indicative of low probability of additional risk

The FEEDAP Panel notes that genotoxicity and carcinogenicity are relevant endpoints for long-living animals (e.g. companion animals, racing horses, reproduction animals), whereas in the case of short-living animals (e.g. animals for fattening) the relevance of these endpoints could be negligible (EFSA SC, 2017). The short lifespan of animal species for fattening under farming conditions makes it very unlikely that these develop cancer as a result of the exposure to genotoxic and/or carcinogenic substances in the diet. Therefore, a comparison of the exposure to these substances with a reference point/threshold based on other (non-neoplastic) endpoints could be more appropriate to assess the safety of the target animals.

For fattening animals, a different magnitude of the MOE(T) (e.g. a MOE(T) > 100 when comparing estimated exposure with a reference point based on non-neoplastic endpoints) or the application of the TTC for non-genotoxic substances is considered more appropriate.

Precondition for the applicability of this approach is the availability of ADME/residue data for the food-producing animal species to consider possible carry-over of genotoxic and/or carcinogenic substances to the animal-derived food products in the assessment of consumer safety.

The FEEDAP Panel underlines that the methodology is applicable only to the risk assessment of additives of botanical origin and cannot be extended to individual compounds intended to be added to feed as such.

The Panel will apply this approach on a case by case basis and may review it in view of the experience gained in the assessment of these additives.

Endorsed by the FEEDAP Panel during the 153rd Plenary meeting of 17-18 March 2021 (link [here](#))

References

EFSA (European Food Safety Authority), 2005. Opinion of the Scientific Committee on a request from EFSA related to a harmonised approach for risk assessment of substances which are both genotoxic and carcinogenic. The EFSA Journal, 282, 1-31

EFSA SC (EFSA Scientific Committee), 2009. Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. EFSA Journal 2009; 7(9):1249, 19 pp. <https://doi:10.2093/j.efsa.2009.1249>

⁴ This will be considered on a case by case basis.

EFSA SC (EFSA Scientific Committee), 2012. Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578, 5 pp.

<https://doi.org/10.2903/j.efsa.2012.2578>

EFSA SC (EFSA Scientific Committee), Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Bresson J-L, Griffin J, Hougaard Benekou S, van Loveren H, Luttik R, Messean A, Penninks A, Ru G, Stegeman JA, van der Werf W, Westendorf J, Woutersen RA, Barizzzone F, Bottex B, Lanzoni A, Georgiadis N and Alexander J, 2017. Guidance on the assessment of the biological relevance of data in scientific assessments. EFSA Journal 2017;15(8):4970, 73 pp.

<https://doi.org/10.2903/j.efsa.2017.4970>

EFSA SC (EFSA Scientific Committee), More SJ, Hardy A, Bampidis V, Benford D, Bennekou SH, Bragard C, Boesten J, Halldorsson TI, Hernandez-Jerez AF, Jeger MJ, Knutsen HK, Koutsoumanis KP, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Nielsen SS, Schrenk D, Solecki R, Turck D, Younes M, Benfenati E, Castle L, Cedergreen N, Laskowski R, Leblanc JC, Kortenkamp A, Ragas A, Posthuma L, Svendsen C, Testai E, Dujardin B, Kass GEN, Manini P, Zare Jeddi M, Dorne J-LCM and Hogstrand C, 2019a. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA Journal 2019;17(3):5634, 77 pp.

<https://doi.org/10.2903/j.efsa.2019.5634>

EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bragard C, Halldorsson TI, Hernandez-Jerez AF, Hougaard BS, Koutsoumanis KP, Machera K, Naegeli H, Nielsen SS, Schlatter JR, Schrenk D, Silano V, Turck D, Younes M, Gundert-Remy U, Kass GEN, Kleiner J, Rossi AM, Serafimova R, Reilly L and Wallace HM, 2019b. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. EFSA Journal 2019;17(6):5708, 17 pp.

<https://doi.org/10.2903/j.efsa.2019.5708>