Meeting

Draft Scientific Opinion on the safety of plant preparations containing berberine

This is a paper for discussion. This does not represent the views of the Committee and should not be cited.

Introduction

1. Following an opinion by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the risks associated with the use of berberine-containing plants as ingredient in food supplements, the European Commission requested EFSA to deliver a scientific opinion on the safety for human consumption of preparations of selected plant species containing berberine. The Panel on Nutrition, Novel Foods and Food Allergens (NDA) assessed the safety of Berberis aquifolium Pursh (root), Berberis aristata DC (root, bark), Berberis vulgaris L. (root, bark), Chelidonium majus L. (herb), Coptis japonica (Thunb.) Makino (rhizome), Coptis teeta Wall. (rhizome), Coptis trifolia (L.) Salisb. (rhizome), Coscinium fenestratum (Goetgh.) Colebr. (root, stem), Hydrastis canadensis L. (rhizome), Jateorhiza palmata (Lam.) Miers (root), Phellodendron amurense Rupr. (bark), Thalictrum flavum L. (root), Tinospora sinensis (Lour.) Merr. (root, stem, leaf). The assessment considered evidence on adverse effects of berberine as a single substance; adverse effects of other alkaloids of the same family as berberine (protoberberine alkaloids), given their high structural similarity with berberine and their co-occurrence in plant species; adverse effects of the whole preparations of the respective plant species, and relevant parts thereof.

2. Medicinal products and novel foods were excluded from the assessment. Moreover, the Panel noted that a risk-benefit analysis was outside the scope of the assessment.

3. The Opinion considered previous evaluations from EFSA, other EU bodies and other regulatory bodies. They noted that EFSA’s Panel on Additives

and Products or Substances used in Animal Feed (FEEDAP) identified a concern for genotoxicity for sanguinarine based on experimental data and a similar concern was identified for chelerytrine, based on the structural similarity with sanguinarine, when evaluating extracts of Macleaya cordata (Willd.) R. Br. for use as feed additives. The EMA also concluded a negative risk- benefit balance for the Chelidonium majus L. (C. majus) herb, based on reports for hepatotoxicity, and potential genotoxicity, cytotoxicity and fetotoxicity. ANSES evaluated the safety of use of berberine-containing plants in the composition of food supplement. Bases on t he recommended use period of 14 days by manufacturers, ANSES opted to establish an acute reference value on the basis of an increase in liver weight in a 2-week study in male rats. Using the LOAEL from that study a human - equivalent LOAEL of LOAEL of 1.25 mg/kg bw berberine per day was determined using allometric scaling. An uncertainty factor of 750 was applied and an indicative toxicity value (iTV)5 for berberine of 1.7 µg/kg bw per day was established. ANSES discouraged the use of berberine supplements in pregnant or breastfeeding women, diabetics, and individuals with hepatic or cardiac disorders, and warned against any concomitant drug treatment due to potential interactions. These recommendations were extended to children and adolescents. Berberine also has a Group 2B classification from IARC, based on carcinogenicity studies in mice and rats, with IARC noting evidence that berberine and its metabolite, berberrubine, can inhibit DNA topoisomerases.

4. With regards to their approach, the Panel outlined the protocol for the evaluation of the safety in use of plant preparations containing berberine (EFSA, 2023. Table 1 outlines the plant species and parts included in the assessment and the Panel also noted that other protoberberine alkaloids present in preparations of these plants are also considered, given their high structural similarity with berberine and their co-occurrence. These include berberastine, berberrubine, columbamine, coptisine, corysamine, demethyleneberberine, epiberberine, fissisaine, groenlandicine, jatrorrhizine, palmatine, stephabine, thalidastine, thalifendine. A systematic search was used for collecting information relevant to the safety assessment, which included human and animal data as well as *in silico* data on genotoxicity. Randomised controlled trials (RCTs) investigating supplementation with berberine or berberine- containing plant preparations and reporting on adverse events in the intervention and control groups were also considered.

5. A call for data was also launched with the aim to gather information on:

- Analytical data on the content of berberine and other protoberberine alkaloids in preparations of plants used in food supplements.
- Use levels recommended by manufacturers for food supplements containing berberine and other protoberberines.
- Biological and toxicological data to support the assessment of a causal relationship between dietary exposure to berberine as single substance and/or in plant preparations and the identified potential adverse effects, including data on absorption, digestion, absorption and metabolism (ADME) for berberine and within the food matrix.
- With regards to exposure, the EFSA Comprehensive European Food Consumption Database was used to provide estimates of exposure to berberine from food supplements in EU populations. The data could not be used based on the limited coverage of botanical food supplements consumption in the database. Data on foods, which contain preparations of the plant species included in the mandate were retrieved from the Mintel Global New Products Database (GNPD). This included information on proposed uses based on manufacturer instructions.

6. A qualitative, expert-guided approach was used to weigh the evidence and draw conclusions regarding the relationship between the exposure to berberine, other protoberberine alkaloids, preparations of the plant species, and the endpoints considered. For genotoxicity, the reliability of the studies was scored using numerical values based on the scoring system by Klimisch et al. (1997). The relevance of the test system and studies were also considered, and they were scored as ‘high’, ‘limited’ or ‘low’ relevance. Additionally, QSAR and read across analysis were used to evaluate the potential genotoxicity of berberine, protoberberines and other alkaloids. This was done using five lines of evidence: quantification of structural similarity using VEGA similarity algorithm; identification of relevant structures in the skeleton of the substances, including structural alerts (SA) specific for mutagenicity, using the ToxRead software, and SAs specific for micronuclei (MN) induction, using the SARpy model; prediction of mutagenicity in Ames test based on CAESAR model, ISS model, SARpy model, kNN model, and VEGA Consensus model; prediction of MN induction in the in vitro MN assay, based on SARpy model, and the in vivo MN assay, based on SARpy and kNN models. The models were used on the following compounds: all protoberberines detected in the plant species as well as other relevant alkaloids, namely canadine and (−)-β-hydrastine, present in preparations of the rhizome/root of H. canadensis, sanguinarine and chelerythrine, present in preparations of the herb of C. majus.

7. With regards to the other endpoints, the internal validity (risk of bias, RoB) of all eligible animal studies identified through the literature search was critically appraised using the Office of Health Assessment and Translation (OHAT) RoB tool developed by the US National Toxicology Program (NTP) (OHAT-NTP, 2019).

8. Section 3.1 of the Opinion addresses the Assessment of berberine and protoberberine alkaloids for which the following data have been considered: characterisation of chemistry, absorption, distribution, metabolism and excretion (ADME), genotoxicity, acute toxicity, general toxicity, developmental toxicity in animals. Mechanistic studies were also considered in each section. For human data, case reports as well as other data from RCTs which reported side effects were considered as well as publications that investigated potential interaction of berberine with medicinal products.

9. Section 3.2 addresses the assessment of Berberis aquifolium (root), for which the following data were considered: information on the characterisation of the plant. No information was retrieved on genotoxicity and general toxicity.

10. Section 3.3 addressed the safety of Berberis aristata (root, bark), for which the following information was considered: characterisation of the plant, genotoxicity, acute toxicity. No information on general genotoxicity was retrieved.

11. Section 3.4 addresses the safety of Berberis vulgaris (root, bark) for which the following information was considered: characterisation of the plant, no information on genotoxicity or general toxicity was available.

12. Section 3.5 addresses the safety of Chelidonium majus (herb) for which the following information was considered: characterisation of the plant, genotoxicity, general toxicity was available, human case reports, interactions with medicinal products.

13. Section 3.6 addresses the safety of Coptis japonica (rhizome) for which the following information was considered: characterisation of the plant, genotoxicity. No general toxicity was available.

14. Section 3.7 addresses the safety of Coptis teeta (rhizome) for which the following information was considered: characterisation of the plant, no information on genotoxicity or general toxicity was available.

15. Section 3.8 addresses the safety of Coptis trifolia (rhizome) for which the following information was considered: characterisation of the plant, no

information on genotoxicity or general toxicity was available.

16. Section 3.9 addresses the safety of Coscinium fenestratum (root, stem) for which the following information was considered: characterisation of the plant, no information on genotoxicity was available, acute toxicity, general toxicity, neurotoxicity.

17. Section 3.10 addresses the safety of Hydrastis canadensis (rhizome, root) for which the following information was considered: characterisation of the plant, genotoxicity (including QSARs on (−)-β-hydrastine and canadine), general toxicity, developmental toxicity, carcinogenicity, human case reports, interactions with medicinal products.

18. Section 3.11 addresses the safety of Jateorhiza palmata (root) for which the following information was considered: characterisation of the plant. no information on genotoxicity or general toxicity was available.

19. Section 3.12 addresses the safety of Phellodendron amurense (bark) for which the following information was considered: characterisation of the plant, genotoxicity, acute toxicity, general toxicity.

20. Section 3.13 addresses the safety of Thalictrum flavum (root) for which the following information was considered: characterisation of the plant, no information on genotoxicity and general toxicity was available.

21. Section 3.14 addresses the safety of Tinospora sinensis (root, stem, leaf) for which the following information was considered: characterisation of the plant, acute toxicity, human case reports. No information on genotoxicity or general toxicity was available.

22. Overall, the Panel reached the following conclusions:

- There is evidence for berberine genotoxicity in vitro, indicating gene mutation and chromosomal damage, which are supported by mechanistic evidence. Confirmation in vivo is lacking, especially at contact sites of exposure, namely the gastrointestinal tract and the liver.
- In view of their high structural similarity with berberine, the genotoxic potential of other protoberberine alkaloids also requires consideration. Available experimental data are sparse and inconclusive.
- Other alkaloids present in the plant preparations included in the mandate, including sanguinarine and chelerythrine in C. Majus, also raise some genotoxic concerns.

- There is no adequate repeated dose toxicity study on berberine alone that would allow identification of a reference point.
- The consumption of berberine-containing food supplements may lead to transient gastrointestinal symptoms such as constipation, diarrhoea, nausea, and abdominal pain.
- Berberine may inhibit CYP3A4 and possibly other CYP450 enzymes, indicating a risk for interaction between berberine-containing plant preparations and various medicinal products.
- Except for H. canadensis, the toxicity profiles of preparations of the plant species included in the mandate, beyond their berberine content, remain largely unknown due to the lack of adequate toxicity studies, resulting in significant uncertainty in the identification and characterisation of hazards associated with these preparations.
- Preparations from rhizome/root of H. canadensis showed evidence of carcinogenic activity in rodents, particularly causing liver adenomas. The mechanisms remain unclear, including potential genotoxic modes of action. The consumption of preparations of rhizome/root of H. canadensis represents a carcinogenic risk for humans.
- The carcinogenic activity of berberine-containing preparations from plants other than H. canadensis has not been studied.
- In humans, consumption of preparations of C. majus aerial parts has been linked to idiosyncratic herb-induced liver injury; susceptible individuals cannot currently be identified, nor can a dose be established below which such reactions would not occur.
- The available data do not allow establishing a safe intake for humans for any preparations of the plant species, and plant parts thereof, included in the assessment.

23. This item is presented for discussion of the COT as a whole. The consultation period closes on 04/05/2026 and therefore the Secretariat welcomes comments until COP 17th of April, after which the Committee comments will be compiled and submitted on behalf of the COT. A summary document will be placed in the collaboration folder for comments, or these can be sent to the Secretariat directly. Please provide page and line numbers in your comment submissions.

Questions to the Committee:

24. Based solely on the information that has been evaluated by EFSA within this Opinion, does the COT agree with the overall conclusions reached for each of the components under assessment?

Does the COT have any comments with regards to the overall scientific methodology, scoring of the studies and weighing of evidence?

Does the COT have any comments on the structure and clarity of the EFSA Opinion?

Does the COT have any other comments?

Secretariat

March 2026

Annex A to TOX/2026/14

Link to the consultation:

Public Consultation PC-1841

Secretariat

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