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Scientific Opinion on taxifolin-rich extract from Dahurian Larch (*Larix gmelinii*)

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Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to carry out the additional assessment for taxifolin-rich extract from Dahurian Larch as a food ingredient in the context of Regulation (EC) No 258/97. The novel food (NF) is a taxifolin-rich water–ethanol extract from the wood of the Dahurian Larch and contains a minimum of 90% taxifolin. The Panel considers that the taxifolin-rich extract is sufficiently characterised and that its compositional data and specifications do not raise safety concerns. The NF is intended to be added to non-alcoholic beverages, to yogurt and to chocolate confectionery. The Panel considers that the data on genotoxicity do not raise concern. In a subchronic rat study performed in accordance with OECD standards, the highest dose tested (i.e. 1,500 mg/kg bw) was considered to be the NOAEL. The margin of exposure (MOE) of the combined intake (158 mg) from the intended food uses (including 100 mg from food supplements) would result to about 660 for an adult weighing 70 kg. For adolescents, taking into account a default body weight of 45 kg, the MOE of the combined intake (146 mg) would be about 460. In the absence of a high percentile intake estimate for children between 9 and 14 years of age, the Panel considers the P97.5 intake estimate from the intended food uses (except from food supplements) for children between 10 and 17 years, i.e. 46 mg/day. Taking into account a default body weight of 29.4 kg (P5 body weight for children aged 10–14 years as suggested by EFSA Scientific Committee (2012)), the resulting MOE would be about 960.

Keywords: taxifolin, (2*R*,3*R*) *trans*-dihydroquercetin, 2,3-dihydroquercetin, Dahurian Larch, novel food, ingredient

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Summary

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to carry out the additional assessment for taxifolin-rich extract from Dahurian Larch as a food ingredient in the context of Regulation (EC) No 258/97 taking into account the comments and objections of a scientific nature raised by the Member States. The assessment follows the methodology set in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods (NFs) and NF ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council. The assessment is based on the data supplied in the original application, the initial assessment by the competent authority of France, the concerns and objections of the other Member States and the responses of the applicant.

The NF is a taxifolin-rich water–ethanol extract from the wood of the Dahurian Larch (*Larix gmelinii* (Rupr.) Rupr) and contains a minimum of 90% taxifolin ((2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one, also called (+) *trans* (2*R*,3*R*)-dihydroquercetin). The Panel considers that the taxifolin-rich extract is sufficiently characterised and that its compositional data and specifications do not raise safety concerns.

The NF is intended to be added to non-alcoholic beverages (at concentrations up to 0.02 g/L), to yogurt (up to 0.02 g/kg) and to chocolate confectionery (up to 0.07 g/kg). The target population for these foods added with taxifolin is the general population from 9 years onwards. In addition, the NF is also intended for food supplements (100 mg/day) for the general population with an age of 14 years and above.

The Panel considers that the data on genotoxicity do not raise concern. In a 90-day subchronic rat study performed in accordance with OECD standards, the highest dose tested (i.e. 1,500 mg/kg body weight (bw)) was considered to be the no observed adverse effect level (NOAEL).

The margin of exposure (MOE) of the combined intake (158 mg) from the intended food uses (including 100 mg from food supplements) would result to about 660 for an adult weighing 70 kg. For adolescents, taking into account a default body weight of 45 kg (P5 body weight for adolescents aged 14–18 years as suggested by EFSA SC (2012)), the MOE of the combined intake (146 mg) would be about 460. In the absence of a high percentile intake estimate for children between 9 and 14 years of age, the Panel considers the P97.5 intake estimate from the intended food uses (except from food supplements) for children between 10 and 17 years, i.e. 46 mg/day. Taking into account a default body weight of 29.4 kg (P5 body weight for children aged 10–14 years as suggested by EFSA Scientific Committee (2012)), the resulting MOE would be about 960. The Panel concludes that the NF, taxifolin-rich extract from Dahurian Larch, is safe under the proposed conditions of use.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

On 23 August 2010, the company Ametis JSC submitted a request under Article 4 of the Novel Food Regulation (EC) No 258/97 to place on the market 'taxifolin' as a novel food (NF) ingredient.

On 2 September 2011, the competent authorities of the United Kingdom forwarded to the Commission their initial assessment report, which came to the conclusion that taxifolin-rich extract may be placed on the market.

On 20 September 2011, the Commission forwarded the initial assessment report to the other Member States. Several of the Member States submitted comments or raised objections.

The concerns of a scientific nature raised by the Member States can be summarised as follows:

- Given that species of the genus *Larix* are not habitually used as a source of food products, it would be advisable for the applicant to carry out an analysis of the 3–4% impurities of the NF on a larger number of more geographically and seasonally diverse lots.
- In the specifications, the applicant indicates that the extract has a minimum taxifolin content of 88%. The initial report indicates that the taxifolin content should be set at 'no less than 90% of the dry weight': accordingly, and in view of the variations that can be expected from the initial raw material, the analytical study of five batches of extract presented by the applicant would appear to be insufficient.
- No information is provided concerning the possible presence of mycotoxins.
- The applicant should carry out regular testing to ensure that the final product is free from mycotoxin contamination. Although the frequency of this testing could be determined by the applicant, the applicant should also ensure that this takes into account the range of yeast and moulds that could be introduced at each stage of production, either via the raw or during storage.
- Documentation certifying the accreditation for one of the testing facilities was not provided.
- Information on the stability of 'taxifolin' in different food matrices should be provided.
- The use of 'taxifolin' as in ingredient added to the intended food categories raises concern regarding children.
- It would be useful to have representative data on the occurrence of taxifolin in foodstuffs of plant origin as well as the resulting estimates for daily intake amounts.
- The intake assessment does not provide figures for high consumers, but assumes that double of the average intake of an adult person equates to the 97.5th percentile.
- The description of an *in vivo* chromosomal aberration test on bone marrow cells of mice had several limitations: insufficient information about control groups, number of animals used; no verification whether 'taxifolin' reached the bones.
- The description of a chromosomal aberration test and a comet assay had similar limitations: use of a positive control group is not described; it is unclear whether both tests were carried out on bone marrow, blood, liver and rectal cells; the dose referred to in the body of the text differs from that in the table.
- The results of the various studies on absorption vary quite considerably. It appears that the bioavailability of the compounds depends on the source and the compounds of the extract, thus 'a specific study should be performed given that the ingredient in question is intended for use in a large number of foodstuffs, and contains reactive compounds liable to have synergistic or antagonistic effects on each other'.
- A mutagenicity study should be carried out in line with the guidelines set out in Commission Recommendation 97/618/EC of 29 July 1997 in the absence of substantial equivalence.
- Several toxicological studies provided used 'taxifolin' from other sources.
- In chronic studies in rats and dogs, only two doses and only male animals were tested. It is unclear whether all required parameters and organs were studied.
- One developmental study had several limitations (no control, unclear method of administration, only one dose tested, start of treatment not clearly described).
- Concerns were expressed whether the toxicological studies have been conducted in accordance with the relevant OECD Guidelines. A 90-day study in rodents in compliance with the specification of the NF and with the 408 OECD Guideline should be conducted. Toxicological study reports are missing. The toxicological information provided is insufficient for deriving an acceptable daily intake (ADI).

- For this type of extract, it is not acceptable to take a supplementary evaluation approach in which each of the family of compounds most abundant in the extract is examined individually in order to draw a conclusion on the overall safety of an ingredient.
- The references and/or study reports of the human studies summarised by the applicant in the application dossier were not provided, nor could they be found in the international specialist literature. It is therefore not possible to assess the bioavailability, allergenicity and metabolism of 'Taxifolin' in humans.
- The studies were conducted in patients to test potential health benefits, but were not designed to test the safety and allergenicity in human. It is impossible to draw conclusions on the safety of 'taxifolin' in human.
- With reference to Zuo et al. (2011), 'Antibacterial and synergy of a flavonol rhamnoside with antibiotics against clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA). Phytomedicine, 18 (11) pp: 990–993', the possible interaction of the product with widely used antibiotics needs to be investigated. Taxifolin belongs to the same chemical class as naringenin, which is known to interact with medicinal substances. Possible interaction with medical substances should be looked into by studying the relevant literature.
- The applicant does not provide confirmation that proteins are absent from the extract, but he claims that the risk of allergenicity is very low.

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Food Safety Authority (EFSA) is asked to carry out the additional assessment of 'taxifolin' as a food ingredient in the context of Regulation (EC) No 258/97.

EFSA is asked to carry out the additional assessment and to consider the elements of scientific nature in the comments raised by the other Member States.

2. Data and methodologies

2.1. Data

The assessment of the safety of this NF ingredient is based on data supplied in the original application, the initial assessment by the competent authority of the United Kingdom, the concerns and objections of the other Member States and the responses of the applicant to these questions and those of the United Kingdom. In accordance with Commission Recommendation 97/618/EC (EC, 1997), taxifolin-rich extract derived from Dahurian Larch is allocated to Class 2.2: 'a complex (non-GM derived) novel food ingredient the source of the novel food having no history of food use in the community'. The data are required to comply with the information required for NFs of Class 2.2, i.e. structured schemes I, II, III, IX, XI, XII and XIII. In its initial assessment report, the competent authority of the United Kingdom came to the conclusion that the range of uses for the novel ingredient is acceptable subject to the implementation of quality control measures described in the applicant's dossier and related to mycotoxin testing. It is noted that the NF ingredient is intended by the applicant to be marketed for its antioxidant properties. This assessment concerns only risk that might be associated with consumption and is not an assessment of the efficacy of 'taxifolin' with regard to any claimed benefit.

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of NFs and NF ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. Assessment

3.1. Specification of the NF

The NF, a taxifolin-rich water–ethanol extract from the wood of the Dahurian Larch (*Larix gmelinii* (Rupr.) Rupr), contains a minimum taxifolin ((2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one, also called (+) *trans* (2*R*,3*R*)-dihydroquercetin) of 90% (Table 1). It is intended to be marketed under the trade name Lavitol®. The NF is a white to pale yellow-coloured powder that crystallises from hot aqueous solutions.

There are two different diastereomers of taxifolin: (2*R*,3*R*)-*trans* and (2*R*,3*S*)-*cis* and the relative enantiomers (2*S*,3*S*) and (2*S*,3*R*). This application refers to (+) *trans* (2*R*,3*R*-dihydroquercetin) form of at least 98% and with no more than 2% of the *cis*-form. The molecular weight of taxifolin is 304.25 Da (CAS No 480-18-2). The identity of the taxifolin has been confirmed using ^{1}H nuclear magnetic resonance spectroscopy and chiroptical methods.

Other components in the NF are very minor and include trace amounts of ethanol, metals, inorganic salts and saponins (Table 2). The usual ranges of components of the NF are provided in Table 3. Saponins are present at levels of below 0.5%.

Table 1: Specification for the novel food ingredient

Specification parameter		Method of analysis*	Limits
Physical parameters	Moisture	GOST* 16,483.7-71	≤ 10%
Compound analysis	Taxifolin (m/m)	MVI 72-08 (HPLC)	≥ 90.0% of the dry weight
Heavy metals, Pesticide	Lead	ICP/MS	≤ 0.5 mg/kg
	Arsenic	ICP/MS	≤ 0.02 mg/kg
	Cadmium	ICP/MS	≤ 0.5 mg/kg
	Mercury	ICP/MS	≤ 0.1 mg/kg
	Dichlorodiphenyltrichloroethane (DDT)	Method 2142-80	≤ 0.05 mg/kg
Residual solvent	Ethanol	USP 32/NF27 <467>	< 5,000 mg/kg
Microbial parameters (equivalent to category 3B, Ph. Eur.) repeated in Section XII.1	Total plate count (TPC)	USP	≤ 10^4 CFU/g
	Enterobacteria + div. Gram-negative bacteria	USP	≤ 100/g
	Yeast and mould	USP	≤ 100 CFU/g
	Escherichia coli	USP	Negative/1 g
	Salmonella spp.	USP	Negative/10 g
	Staphylococcus aureus	USP	Negative/1 g
	Pseudomonas spp.	USP	Negative/1 g

HPLC: high-performance liquid chromatography; ICP/MS: Inductively coupled plasma mass spectrometry; CFU: colony-forming units.
*: GOST (GOsudarstvenniy Standard, Russian State Standard.

Table 2: Batch analysis results of the Novel Food ingredient based on five non-consecutive batches extracted from Dahurian Larch

Specification parameter	Specification	Batch 2	Batch 27a	Batch 29b	Batch 66a	Batch 950
Outward appearance	White or straw-coloured powder	Conform	Conform	Conform	Conform	Conform
Moisture	≤ 10%	7.85%	7.85%	4.55%	9.6%	7.85%
Taxifolin (% of the dry weight)	≥ 90%	92.20%	92.43%	92.36%	92.58	92.20%
Lead (mg/kg)	≤ 0.5 mg/kg	0.001	0.067	0.001	0.043	0.040
Arsenic (mg/kg)	≤ 0.02 mg/kg	< 0.001	0.002	< 0.001	0.004	0.003
Cadmium (mg/kg)	≤ 0.5 mg/kg	0.001	0.028	< 0.001	0.028	0.040
Mercury (mg/kg)	≤ 0.1 mg/kg	< 0.001	0.010	< 0.001	0.006	0.011
Dichlorodiphenyltrichloroethane (DDT) (mg/kg)	≤ 0.05 mg/kg	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
Ethanol (mg/kg)	< 5,000 mg/kg	197.2	147.1	121.8	177.4	31.5

Table 3: Usual range of components of the NF (as per dry substance)

Extract component	Content, usual observed range (%)
Taxifolin	90–93
Aromadendrin	2.5–3.5
Eriodictyol	0.1–0.3
Quercetin	0.3–0.5
Naringenin	0.2–0.3
Kaempferol	0.01–0.1
Pinocembrin	0.05–0.12
Unidentified flavonoids	1–3
Water*	1.5

*: Taxifolin in its hydrated form and during the drying process is a crystal. This results on the inclusion of water of crystallisation in a quantity of 1.5%.

According to the certificate issued by the laboratory performing the test for residual protein, protein could not be detected in 10 lots of the NF. In response to EFSA's request to provide information on the applied method for analysing the presence of residual protein, the applicant informed that the limit of quantification (LOQ) was 0.3 mg/g analysed with the Kjeldahl method in accordance with §64 LFGB L06.00-7 (German legislation).

The UK Committee referred to the nature of the raw material and asked the applicant whether the product was tested for the presence of mycotoxins. The applicant indicated that they did not routinely test for mycotoxins, but the quality control (QC) systems employed in the selection of the raw material, coupled with routine testing for yeasts and moulds in the resulting sawdust, are adequate. Ten randomly selected batches of a taxifolin extract, manufactured from January through October of 2011, were tested in the presence of aflatoxins. No aflatoxins were found. The Panel accepts that the QC system is adequate.

The Panel considers that the taxifolin-rich extract is sufficiently characterised and that its compositional data and specifications do not raise safety concerns.

3.2. Effect of the production process applied to the NF

The applicant provided certificates that the applicant is ISO 9001:2000 certified for the production of food and food additives. Stumps of Dahurian Larch wood are sawed, debarked, chopped and shaved and the ground shavings are dried. The ground wood mass is extracted with 75–80% ethanolic aqueous solution. The solvent is removed from the extract with vacuum distillation. Taxifolin is crystallised after addition of water. The final product is dried (moisture $< 10\%$) using vacuum distillation and packaged with taxifolin content of not less than 90%.

The stability of the NF ingredient in the containers for marketing (dark glass bottles) was tested for 3 months under normal conditions (25°C, 65% RH), and for 24 weeks under stressed conditions (40°C, 75% RH). After storage at 40°C, the amount of taxifolin was 94.5% and 97.5% after 1 week and after 30 weeks, respectively. In response to the Member States' comments, the applicant provided some additional information on the stability of taxifolin in foods. After 1 year of storage of soymilk concentrate fortified with taxifolin, there was a decrease in the taxifolin content: at 4°C by −6.8%, at 10°C by −3.2% and at 20°C by −10.3%.

The Panel considers that the production process and the stability are sufficiently described and do not raise safety concerns.

3.3. History of the organism used as the source of the NF

The Panel notes that the source of the NF, Dahurian Larch, *Larix gmelinii* (Rupr.) Rupr., has no history of food use.

3.4. Anticipated intake/extent of use of the NF

The applicant originally intended the NF for the use in a wide range of food products including food supplements and PARNUTS. Following a request from EFSA to revise the anticipated intake, the applicant decided to modify the intended use categories (Table 4). According to the applicant, the NF

is intended for the general population from the age of 9 years onwards, with the exception of its use for food supplements which are not intended for children of below 14 years of age.

Table 4: Updated intended uses and use levels for the NF as food ingredient

Food category	Proposed food use	Proposed max use levels within these foods as food ingredient (g/L or g/kg)
Beverages[(a)]	Non-alcoholic beverages	0.02 g/L
Milk products[(a)]	Yogurt, ca. 7.5% fat (0.025% by fat mass)	0.02 g/kg
Sugar, preserves, confectionery[(a)]	Chocolate confectionery, ca. 35% fat (0.02% by fat mass)	0.07 g/kg
Dietary supplements[(b)]		100 mg/day

(a): Intended for the general population from the age of 9 years onwards.
(b): Intended for the general population from the age of 14 years onwards.

For the revised intake estimate, the applicant used the spread-sheets[1] for chronic consumption available at the EFSA website on summary statistics of the EFSA Comprehensive Food Composition database (EFSA, 2011). The intake was calculated for all intended consumer groups (Table 5).

Table 5: Estimated intake levels of taxifolin for the intended food categories and target groups* (children are included upon EFSAs request although they are not among the target groups)

	Food category	Use level (g/kg)	Mean (mg/day)	95th percentile (mg/day)	97.5th percentile (mg/day)
Adolescents (from 10 years up to 17 years of age)	Non-alcoholic beverages	0.0250	10.5	20.4	30.3
	Flavoured fermented milk and dairy products	0.019	2.4	5.8	7.5
	Chocolate products	0.070	2.5	7.6	8.4
	Combined consumption levels for all three categories		15.4	33.8	46.2
Adults (≥ 18 years of age)	Non-alcoholic beverages	0.0250	9.4	28.8	36.4
	Flavoured fermented milk and dairy products	0.019	4.1	11.2	13.9
	Chocolate products	0.070	2.3	6.0	7.7
	Combined consumption levels for all three categories		15.8	46.0	58.0

*: The applicant based its estimates on 'consumers only'.

Considering a daily intake of 100 mg taxifolin from supplements and by taking into account the 97.5th percentile intake estimate from the other intended uses (Table 4), the combined intake from all intended food uses would result to 158 mg for an adult and 146.2 mg adolescents.

The Panel notes that the intake estimate was performed with use levels of the NF which slightly deviate from the intended use levels (intended use level for beverages: 0.02 g/L vs use level used for the intake assessment: 0.025 g/L and 0.02 g/kg for yogurt vs 0.019 g/kg for fermented milk products). The applicant noted that despite that all 'flavoured fermented milk and dairy products fermented milk' as a whole food category was used for the intake estimate the NF is only intended to be used for yogurts from this category. The Panel also notes the conservative approach and assumptions applied in the applicant's intake estimate (i.e. use of 'consumers only', food categories

[1] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

used, summing up the high percentiles of each category for deriving the high percentiles for the intake from all categories.)

3.5. Information from previous exposure to the NF

In response to the Member States' questions, the applicant provided some information on the occurrence of taxifolin enantiomers in foods of plant origin. Taxifolin is present in apple flesh (1,300 mg/kg) and apple skin (7,400 mg/kg) (Vega-Villa et al., 2009). The most abundant taxifolin enantiomers in apple skin corresponded to the (2*R*,3*S*)-(−)glycoside (41% of the total taxifolin) and the (2*S*,3*R*)-(+)aglycone (17% of the total taxifolin) (Vega-Villa et al., 2009). Also, other foods have been reported to contain taxifolin such as red onions (98 mg/kg; Slimestad et al., 2007), tomato, olive oil, sorghum grain, white grapes, strawberries, mulberries (21 μg/g FW; Zhang et al., 2008), acai, peanuts, pine seeds (172 mg/100 g; Lantto et al., 2009), thyme, citrus fruits, white wine and beer (1 mg/L; Gerhäuser, 2005). With regard to the concerned (+)2*R*,3*R*-diastereoisomer, information about its occurrence in foods has been provided only for tomatoes (27% of total taxifolin) and apple (< 0.03% of total taxifolin) (Vega-Villa et al., 2009, 2011) with most of the taxifolin stereoisomers present as glycosides.

The applicant provided a list of 57 food supplements containing taxifolin from the Dahurian Larch. The applicant claimed that by April 2009, over 250 products containing taxifolin were registered with the regulatory bodies of the Russian Federation. Among these products, 142 were food supplements, over 40 were other food products and over 70 were cosmetic products, recommended adult dosages range from 5 to 100 mg of taxifolin per day. The applicant provided sales figures and stated that 18 tonnes of taxifolin (from larch wood) were sold by the applicant to be used within dietary supplements mainly in Russia, Switzerland, USA and Canada.

3.6. Nutritional information on the NF

Considering the composition and the anticipated daily intakes of the novel food ingredient, the Panel considers it unlikely that the consumption of the NF would be nutritionally disadvantageous.

3.7. Microbiological information on the NF

The final product is routinely tested to confirm the absence of a number of pathogenic microorganisms in accordance with the European Pharmacopeia. Analysis of five batches demonstrated compliance with the specification (Table 1). The Panel considers that microbiological information does not raise safety concerns.

3.8. Toxicological information on the NF

The application describes a number of safety studies and, in response to questions raised by the Member States, the applicant confirmed that the subchronic and reproductive toxicity studies were carried out with their taxifolin product. Other studies had used taxifolin preparations from other manufacturers, using the same or very similar methods of extraction. The applicant also provided the specification of the taxifolin extract used by Shkarenkov et al. (1998), who carried out a number of the toxicological studies cited in the application. This extract contained comparable amounts of taxifolin and other identified flavonoids to the applicant's product.

3.8.1. Genotoxicity

After submission of the original application a number of genotoxicity studies complying with the rules of Russian Good Laboratory Practice (GLP) (issued by the Ministry of Health of the Russian Federation) have been submitted with the NF. None of these studies were conducted following OECD Guidelines.

In an Ames test with only three strains of *Salmonella* Typhimurium (TA100, TA98 and TA97) using the plate incorporation method, taxifolin induced an increase in the number of revertant colonies at the highest dose tested (1,000 μg/plate) in the presence of a metabolic activation system (S9 mix) and a dose-related increase at the two highest doses (500 and 1,000 μg/plate) in the absence of S9 mix in strains TA97 and TA98 (Durnev, 2011a).

No effect of taxifolin was seen in an *in vivo* comet assay in the bone marrow, liver and blood of mice (Durnev, 2011b), an *in vivo* chromosomal aberration test using mice (Durnev, 2011c), and a

genotoxicity study in *Drosophila melanogaster* (Durnev, 2011d). The Panel considered that these studies contained considerable weaknesses and requested new studies to be performed in accordance with the respective OECD test guideline. In response, the applicant provided a bacterial reverse mutation test (OECD TG 471) (Ametis, 2013a) and an *in vitro* micronucleus test in human lymphocytes (OECD TG 487) (Ametis, 2013b).

The NF was tested for its potential to induce gene mutations in the bacteria reverse mutation assay (Ametis, 2013a). The test substance Lavitol (93.7% purity) was tested (using the plate incorporation method) in the *Salmonella* Typhimurium strains TA1535, TA1537, TA98, TA100 and the *Escherichia coli* strain WP2uvrA (pKM101) at dose levels up to 5,000 μg/plate, both with and without the addition of S9-mix. The test item was dissolved in dimethyl sulfoxide (DMSO). Appropriate positive and negative controls were included. The study was performed according to GLP and OECD test guideline 471.

Toxicity was observed in all strains at the highest dose level evident as a reduction in the growth of the bacterial background lawn. In two independent experiments, dose-related increases in the number of revertant colonies were obtained for strains TA98 and TA1537 and to a lesser extent for TA100 in both the presence and absence of S9-mix. The Panel concludes that the NF showed clear evidence of mutagenic activity under the test conditions used.

The NF was tested for its ability to induce micronuclei in cultured human peripheral blood lymphocytes (Ametis, 2013b). Human lymphocyte cultures were exposed to Lavitol (93.7% purity) for 3 h in the presence and absence of S9-mix, and for 20 h in the absence of S9-mix. The vehicle was DMSO. The study was performed according to GLP and OECD test guideline 487. The concentrations used in the main micronucleus test were selected based on preliminary cytotoxicity tests by calculating the cytokinesis-block proliferative index (CBPI). In the main test, the highest concentrations selected for micronucleus analysis were 650 μg/mL for the 3-h treatment in the presence and absence of S9-mix (57.8% and 58.0% cytotoxicity, respectively), and 200 μg/mL for the 20-h treatment in the absence of S9-mix (53.5% cytotoxicity). No increases in the frequency of micronucleated cells were seen. The Panel concludes that the NF was neither clastogenic nor aneugenic under the test conditions used.

At request from EFSA for an additional *in vivo* genotoxicity study, the applicant also provided a comet assay to assess the potential of taxifolin to induce DNA strand breaks in the colon, duodenum and liver of Crl:CD (SD) rats (Ametis, 2015). Animals were treated orally with taxifolin at dose levels of 500, 1,000 and 2,000 mg/kg per day on three occasions with the second dose being administered approximately 24 h after the first dose, and with the third dose being administered approximately 21 h after the second dose, 3 h before sampling. As no mortalities or clinical signs of reaction were observed between the sexes in a preliminary toxicity test, the comet test was performed using male animals only. All animals were dosed orally using a dose volume of 10 mL/kg. The vehicle control group received purified water and the positive control group received ethyl methanesulfonate (EMS) at 200 mg/kg. No statistically significant increases in the median % tail intensity (TI) were observed in either the colon, duodenum or liver of male Crl:CD(SD) rats administered Lavitol at any dose level, compared to vehicle control values. The positive control compound, EMS, produced statistically significant increases of 48% in the group mean median % TI when compared to vehicle control values. Some small incidences of bodyweight loss were observed across all groups in the comet test on Day 3. The Panel concludes that taxifolin did not cause an increase in DNA strand breaks or cytotoxicity in the colon, duodenum or liver of male Crl:CD (SD) rats.

Overall, the Panel notes that the NF was positive for mutagenic activity in the bacterial reverse mutation test. An *in vitro* micronucleus test showed a negative outcome. The genotoxic potential was further investigated in an adequately performed *in vivo* genotoxicity test in three tissues (comet assay) with a negative outcome. The Panel notes that the approach followed the 'EFSA Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment' (EFSA SC, 2011). The Panel concludes that the NF is not considered to be of genotoxic concern.

3.8.2. Absorption, distribution, metabolism, excretion

The Panel notes that none of the absorption, distribution, metabolism, excretion (ADME) studies were testing the NF as specified in this application.

In general, large differences in the bioavailability of taxifolin in rats have been reported. In one study, trace amounts of taxifolin were detected in rat plasma after oral administration (10–100 mg/kg body weight (bw)). Plasma taxifolin was measured in samples obtained 3, 6, 10, 15, 20, 25, 30, 40, 50, 60, 90, 120, 150, 180, 240 and 300 min after dosing. When compared with intravenous administration, a bioavailability figure of 0.17% was calculated (Wang et al., 2009).

In another rat study with taxifolin produced by the applicant, male rats were given 12.5, 25 or 50 mg taxifolin/kg bw by single oral administration or 50 mg/kg bw by intravenous administration (Seredin et al., 2007). In this study, taxifolin given orally was rapidly absorbed from the gastrointestinal (GI) tract, and reached a maximum concentration in the blood plasma after 30 min with undetectable levels after 8 h. Taxifolin was detectable at highest concentrations not only in the blood plasma and kidneys but also in the liver heart, spleen, brain, skeletal muscles, lungs for up to 24 h after administration (Seredin et al., 2007). In this study, the bioavailability of taxifolin compared to intravenous administration was 24%.

High-performance liquid chromatography (HPLC) analysis of rat urine by Seredin et al. (2007) found a number of peaks which corresponded to derivatives of taxifolin. The authors report that around 8% of the original dose given orally (50 mg/kg bw) was seen in urine during the first 24 h after administration, but none was seen in the following 24 h. No taxifolin was detected in the faeces after 24 and 48 h. In a separate study (Voskoboinikova et al., 1993), the urinary excretion of taxifolin over a 24-h period did not exceed 6% of the intravenous dose administered, with a near linear increase with dose.

A study (Brown and Griffiths, 1983) reported the conversion of taxifolin to 3'- or 4'-*O*-methyltaxifolin in rats.

Another study in two human volunteers consuming 2 g of taxifolin reported its conversion into a number of hydroxyphenylacetic acids. It was reported that the same metabolites were excreted as in similar experiments with quercetin (Booth and De Eds, 1957).

The bioavailability of taxifolin in rabbits was 36% after ingestion of 8–80 mg/kg bw (Pozharitskaya et al., 2009).

Taxifolin was rapidly absorbed in rats from the GI tract. Absorbed taxifolin was distributed to the blood plasma, liver, heart, spleen, brain, skeletal muscles, lungs and kidneys. Metabolites of taxifolin are excreted through the urine. Excretion of unaltered taxifolin through urine is low.

3.8.3. Acute and subacute toxicity

The toxicity of a taxifolin-rich extract from larch was assessed following single intragastric administration to rats and mice in doses up to 12,000 mg/kg bw (Shkarenkov et al., 1998). Intragastric administration of a single dose of 12,000 mg/kg bw resulted in no animal deaths.

As a response to the Member States' comments, the applicant has provided a subacute study in rats. The compound tested in this study is a commercial product, which is in conformity with the specifications of the NF.

In the subacute study, groups of 20 Wistar rats (10/sex) were given 10,000 or 15,000 mg NF/kg bw by gavage for 7 days (Celyico, 2008). All animals survived but soft stools and porphyrin around the eyes were seen in some test animals (no individual data). Erythrocyte counts in female rats were statistically significantly lower in the two dose groups compared to the control group, 6.8 and 6.7 vs 9.6 (10^{12}/L). No effect on erythrocytes was seen in male rats. No differences between groups were seen for the urinalysis and the organ weights. 'Oedema' in a non-specified part of the gastrointestinal tract was observed in 11 rats from both dose groups and one rat from the control group. Oedema of the liver was seen in four rats from both dose groups. Slight foci of fresh haemorrhage and heterogeneous nuclei of cardiomyocytes were seen in rats from test and control groups. No information about severity was provided. The Panel notes the high doses tested.

3.8.4. Subchronic toxicity

In the original dossier, the applicant provided a 90-day study which did not meet OECD standards and was therefore considered by the Panel not suitable to draw conclusions on the subchronic toxicity in rats.

As a response to an EFSA request for a 90-day study in accordance with OECD standards, the applicant has provided a new subchronic study in rats. The compound tested taxifolin with a purity of 90.5%.

In the study, groups of 20 rats (Wistar albino rats) (10/sex) were given 0, 50, 150 or 1,500 mg Lavitol/kg bw for 90 days (Tselyico, 2016 – unpublished study report). In addition, a high-dose recovery group and a control recovery group of 5 rats/sex were observed during a 28-day treatment-free period. The rats were about 8 weeks old at the start of the study. The Lavitol was dissolved in a 1% starch solution and administered orally via a stomach tube. The study complies with OECD test guideline no 408 (1998) and followed the rules of GLP (issued by the Ministry of Health of the Russian Federation). The animals were housed 5/sex per cage and fed a natural-ingredient diet.

No mortality was seen during the study. Occurrence of aggression was seen in two females and three males from the high-dose group and in one female and two males of the mid-dose groups. In the control groups, aggressive behaviour was only seen in one female. For the female rats, this can be related to the significant increase in the occurrence of abrasions, which was seen in the high-dose females and judged to be caused by fighting between the animals. The presence of five animals per cage could be a contributing factor behind these observations. No difference in body weight was seen between the male and female groups. In males, the absolute weight gain was significantly lower in the high-dose group compared to controls from day 1–90, and in the recovery groups from day 1–118. Food consumption was not significantly different between groups but tended to be lower in the high-dose male group compared with the control group. The lower body weight gain seen in high-dose males could be consequence of the lower feed intake and also the observed lower initial body weights of this group.

No difference in the ophthalmological examination, the results of electrocardiogram and behavioural activity were seen between the groups. No statistically significant differences were seen between the control and the Lavitol-dosed groups in haematology parameters, except for a significant increase in platelet counts for the low-dosed males. In the female recovery groups, a significant higher leucocyte count was seen in the high-dose group, and in males, a significant increase in RBC was seen for the high-dose group. In clinical biochemistry, alkaline phosphatase was significantly higher in the low-dose males and level of triglycerides was significantly lower in the female mid-dose group. In the recovery period, triglyceride level was significantly lower in the high-dosed females. No differences were seen between the male groups. Urinalyses and relative organ weights showed no statistically significant differences between groups. Absolute organ weights were only displayed on an individual level. The gross pathological examination showed deformation of the fundus of the stomach in one high-dosed male and female, and in one male from the high-dose recovery group. No stomach-related findings were seen in the other groups. The stomach-related findings were supported by microscopic observations found to be pronounced hyperaemia of the capillaries of the mucosa, moderate oedema and infiltration of the submucosa, thickening of the serous membranes and inflammatory infiltration of the surface layer of the mucous membrane and could result from an irritating effect on the stomach mucosa due to the application of test material directly into the stomach. Hypertrophy of the adrenal glands was seen in two male and two female rats from the high-dose group and in one male and female from the high-dose recovery group. The adrenal hypertrophy was also seen in one female control and one low-dose male and female. The adrenal findings were supported by the microscopic examination, which were described as an increase in the mass of cortical and medullar substances, small haemorrhage around small arteries and capillaries. The macroscopic findings in the adrenals and stomach could be explained by aggressive behaviour leading to stress and local irritation, respectively. Furthermore, the incidences are small, also found in the control group and are not supported by other findings. The Panel therefore considers that the no observed adverse effect level (NOAEL) of the study is 1,500 mg/kg bw per day, the highest dose tested.

3.8.5. Developmental toxicity

As a response to the Member States' comments, the applicant has provided a developmental toxicity study in rats. The compound tested is a commercial product, which is in conformity with the specifications of the NF.

In the developmental toxicity study, groups of 20 pregnant female rats (*Rattus norvegicus*) were given 0, 75 or 1,500 mg NF/kg bw during gestation day from 6 to 16. An additional group was given 75 mg NF/kg bw during gestation day from 1 to 19 (Celyico, 2011). The rats were about 3 months old at the start of the study. The test compound was dissolved in a 1% starch solution and administered orally via a stomach tube. Endpoints included, for dams, clinical signs, mortality, body weight, functional observations, clinical chemistry, fetal survival, and gross, skeletal and visceral examination of fetuses, for the offspring, body weight, sensory motor evaluation, clinical chemistry and necropsy and histopathological examination were carried out. The study complies with the rules of GLP (issued by the Ministry of Health of the Russian Federation). The study design is very similar to the one proposed in OECD TG 414. All dams survived and no signs of toxicity were observed during the prenatal dosing. The administration of the NF caused no effects to the fetuses regarding litter size, weight, formation of organs and general development. No embryotoxic or teratogenic effect of the NF was seen in the study at dose level up to 1,500 mg/kg bw.

3.8.6. Human studies

The applicant provided a summary on 15 human studies with in total 18 study arms in which taxifolin (from larch) was administered to patients with a relatively wide range medical conditions, including atherosclerosis, arterial hypertension, ischaemic heart disease, vascular encephalopathy, diabetes, Lyme disease, patients awaiting operations on ovaries and chronic pulmonary obstructive diseases. According to the tabulated summary provided by the applicant, taxifolin was administered in addition to a standard therapy for the underlying disease. The applicant states that in total 507 patients were given taxifolin (40–120 mg/day) for 2 weeks to 3 months and no side effects were reported.

The Panel considers that no conclusions on the safety can be made from the information provided.

3.8.7. Allergenicity

Cases on occupational allergenicity to larch wood dust have been reported (Kespohl et al., 2012). According to the applicant, allergenicity to the NF has not been reported from Russia, Switzerland, USA and Canada where the NF is marketed.

According to the information provided in Section 1 (Specifications), protein was not detected at a LOQ of 0.3 mg/g. Considering the production process, which includes crystallisation and estimated intake of the NF, the amount of protein intake from the NF would be very low, i.e. less than 47 μg (considering the high percentile intake estimate for adults, i.e. 158 mg).

Based on this information, the Panel considers that the likelihood of allergenicity is low.

4. Discussion

The NF is a taxifolin-rich water–ethanol extract from the wood of the Dahurian Larch (*Larix gmelinii* (Rupr.) Rupr) and contains a minimum of 90% taxifolin ((2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2, 3-dihydrochromen-4-one, also called (+) *trans* (2*R*,3*R*)-dihydroquercetin). The Panel considers that the taxifolin-rich extract is sufficiently characterised and that its compositional data and specifications do not raise safety concerns.

The NF is intended to be added to non-alcoholic beverages (at concentrations up to 0.02 g/L), to yogurt (up to 0.02 g/kg) and to chocolate confectionery (up to 0.07 g/kg). The target population for these foods added with taxifolin is the general population from 9 years onwards. In addition, the NF is also intended for food supplements (100 mg/day) for the general population with an age of 14 years and above.

The Panel considers that the data on genotoxicity do not raise concern. In a 90-day subchronic rat study performed in accordance with OECD standards, the highest dose tested (i.e. 1,500 mg/kg bw) was considered to be the NOAEL.

The margin of exposure (MOE) of the combined intake (158 mg) from the intended food uses (including 100 mg from food supplements) would result to about 660 for an adult weighing 70 kg. For adolescents, taking into account a default body weight of 45 kg (P5 body weight for adolescents aged 14–18 years as suggested by EFSA SC (2012)), the MOE of the combined intake (146 mg) would be about 460. In the absence of a high percentile intake estimate for children between 9 and 14 years of age, the Panel considers the P97.5 intake estimate from the intended food uses (except from food supplements) for children between 10 and 17 years, i.e. 46 mg/day. Taking into account a default body weight of 29.4 kg (P5 body weight for children aged 10–14 years as suggested by EFSA Scientific Committee (2012)), the resulting MOE would be about 960.

5. Conclusions

The Panel concludes that the NF food, taxifolin-rich extract from Dahurian Larch, is safe under the proposed conditions of use.

Documentation provided to EFSA

1) Letter from the European Commission to the European Food Safety Authority with the request for an opinion on the safety of 'taxifolin'. SANCO E6/AK/bs Ares (2012)1443458 dated 5 December 2012.

2) Dossier on 'Taxifolin' submitted by Ametis. Received on 5 December 2012. Additional information was submitted on 11 and 13 December 2013, 2 March, 12 August and 28 September 2015, 19 July and 24 October 2016.
3) Initial assessment report carried out by the United Kingdom: 'Advisory Committee for Novel Foods and Processes. Opinion on a taxifolin-rich extract from Dahurian Larch'. Assessment of safety for the consumer, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients (August 2011).
4) Member States' comments and objections.
5) Response by the applicant to the initial assessment report and the Member States' comments and objections.

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Ametis, 2015. Report Lavitol® (Dihydroquercetin) Crl:CD(SD) Rat *in vivo* comet test. Huntingdon Life Sciences (HLS) study number: NID0003, Final Report, 28 January 2015.

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Abbreviations

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, excretion
bw	bodyweight
CAS	Chemical Abstracts Service
CBPI	cytokinesis-block proliferative index
CFU	colony-forming units
DDT	dichlorodiphenyltrichloroethane
DMSO	dimethyl sulfoxide
EMS	ethyl methanesulfonate
FW	Fresh weight
GI	gastrointestinal
GLP	Good Laboratory Practice
GOST	GOsudarstvenniy Standard (Russian State Standard)
HPLC	high-performance liquid chromatography
ICP/MS	inductively coupled plasma mass spectrometry
ISO	International Organization for Standardization
LOQ	limit of quantification
MOE	margin of exposure
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
NF	novel food
NOAEL	No observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
QC	quality control
TI	tail intensity
RBC	Red blood count
TPC	total plate count