

SCIENTIFIC OPINION

Scientific opinion on the safety and efficacy of L-tyrosine for all animal species¹

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)^{2,3}

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ABSTRACT

L-Tyrosine can be synthesised in the body from L-phenylalanine, an essential amino acid. The additive L-tyrosine is produced by acid hydrolysis of feather keratin. L-Tyrosine is considered safe for all animal species, provided that the conditions of use are respected, i.e. supplementation of conventional diets with 0.5 % L-tyrosine for food-producing animals and 1.5 % for non-food-producing species. Higher dietary concentrations may lead to growth rate depression and eye lesions, and, in young animals, behavioural changes. L-Tyrosine will be incorporated into the body protein of the animal. The protein composition will not be changed. Free L-tyrosine will not be stored in the tissues. On the basis of the data available, no risk is expected for the consumer from the use of this L-tyrosine preparation showing a purity > 95 %. In the absence of data, the product is considered potentially irritating to skin and eyes, a potential dermal sensitiser and hazardous by inhalation. The use of L-tyrosine in animal nutrition would not be expected to lead to any localised increase in the concentration of L-tyrosine or its metabolites in the environment. It is concluded that the use of this product as a feed additive does not represent a risk to the environment. The supplementation of feed with L-tyrosine is efficacious in cases where high requirements for tyrosine as a melanin precursor occur. This has been demonstrated in cats for intensively colouring the coat. L-Tyrosine may also have the potential to intensify the pigmentation of the coat/plumage of other species, but limited evidence is available.

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KEY WORDS

nutritional additive, amino acid, L-tyrosine, L-phenylalanine, melanin, coat pigmentation

¹ On request from the European Commission, Question No EFSA-Q-2010-01312, adopted on 20 June 2013.

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³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Amino Acids, including Paul Brantom, Noël Dierick and Jürgen Gropp, for the preparatory work on this scientific opinion.

Suggested citation: EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2013. Scientific opinion on the safety and efficacy of L-tyrosine for all animal species. EFSA Journal 2013;11(7):3310, 18 pp. doi:10.2903/j.efsa.2013.3310

Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following a request from the European Commission, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the safety and efficacy of L-tyrosine for all animal species.

Tyrosine can be synthesised in the body from phenylalanine, an essential amino acid. The additive L-tyrosine is produced by acid hydrolysis of feather keratin.

L-Tyrosine is considered safe for all animal species, provided that the conditions of use are respected, i.e. supplementation of conventional diets with 0.5 % L-tyrosine for food-producing animals and 1.5 % for non-food-producing species. Higher dietary concentrations may lead to growth rate depression and eye lesions, and, in young animals, behavioural changes.

L-Tyrosine will be incorporated into the body protein of the animal. The protein composition will not be changed. Free L-tyrosine will not be stored in the tissues. On the basis of the data available, no risk is expected for the consumer from the use of this L-tyrosine preparation showing a purity > 95 %.

In the absence of data, the product is considered potentially irritating to skin and eyes, a potential dermal sensitiser and hazardous by inhalation.

The use of L-tyrosine in animal nutrition would not be expected to lead to any localised increase in the concentration of L-tyrosine or its metabolites in the environment. It is concluded that the use of this product as a feed additive does not represent a risk to the environment.

The supplementation of feed with L-tyrosine is efficacious in cases where high requirements for tyrosine as a melanin precursor occur. This has been demonstrated for cats for intensively colouring the coat. L-Tyrosine may also have the potential to intensify the pigmentation of the coat/plumage of other species, but limited evidence is available.

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BACKGROUND

Regulation (EC) No 1831/2003⁴ establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 4(1) of that Regulation lays down that any person seeking authorisation for a feed additive or for a new use of a feed additive shall submit an application in accordance with Article 7.

The European Commission received a request from the company BCF (Bretagne Chimie Fine)⁵ for authorisation of the product L-tyrosine – food grade, when used as a feed additive for all animal species (category: nutritional additives; functional group: amino acids, their salts and analogues) under the conditions mentioned in Table 1.

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 4(1) (authorisation of a feed additive or new use of a feed additive). EFSA received directly from the applicant the technical dossier in support of this application.⁶ According to Article 8 of that Regulation, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. The particulars and documents in support of the application were considered valid by EFSA as of 07 January 2011.

The additive ‘L-Tyrosine – food grade’ is a preparation of L-tyrosine obtained by hydrolysis of natural keratin (from poultry feathers) and further purification. This product has not been previously authorised as an amino acid in the European Union

L-Tyrosine is approved as a human food additive and is used in particular nutrition, e.g. in baby food, according to the Commission Directive 2006/141/EC to achieve the correct protein level in the finished products.⁷

The Joint FAO/WHO expert committee of Food Additives (JECFA, 2005) assessed L-tyrosine when used as a flavouring and no concern for consumer safety was identified. The Panel on Dietetic Products, Nutrition and Allergies (NDA) of EFSA issued a scientific opinion on the substantiation of health claims related to L-tyrosine and contribution to normal synthesis of catecholamines, increased attention, and contribution to normal muscle function pursuant to Article 13(1) of Regulation (EC) No 1924/2006⁸ (EFSA, 2011).⁸

TERMS OF REFERENCE

According to Article 8 of Regulation (EC) No 1831/2003, EFSA shall determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and the efficacy of the product L-tyrosine (L-tyrosine, food grade), when used under the conditions described in Table 1.

⁴ 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.

⁵ Bretagne Chimie Fine, Boisel, 56140 Pleaucadeuc, France.

⁶ EFSA Dossier reference: FAD-2010-0260.

⁷ Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC. OJ L 401, 30.12.2006, p. 33.

⁸ Regulation EC No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 17.

Table 1: Description and conditions of use of the additive as proposed by the applicant

Additive	L-TYROSINE
Registration number/EC No/No (if appropriate)	/
Category(-ies) of additive	nutritional
Functional group(s) of additive	amino acids, their salts and analogues

Description			
Composition, description	Chemical formula	Purity criteria (if appropriate)	Method of analysis (if appropriate)
L-Tyrosine	$C_9H_{11}NO_3$	L-Tyrosine content not less than 95.0 % on the additive	dosage in feedingstuffs: HPLC, Commission regulation (EC) No 152/2009

Trade name (if appropriate)	L-Tyrosine – food grade
Name of the holder of authorisation (if appropriate)	Bretagne Chimie Fine

Conditions of use				
Species or category of animal	Maximum Age	Minimum content	Maximum content	Withdrawal period (if appropriate)
		mg/kg of complete feedingstuffs		
all animals	-	-	-	-

Other provisions and additional requirements for the labelling	
Specific conditions or restrictions for use (if appropriate)	/
Specific conditions or restrictions for handling (if appropriate)	As for any powder product which may generate dust, wear a mask, goggles and safety glasses
Post-market monitoring (if appropriate)	not considered necessary in view of adequate production and control procedures during the manufacturing process to ensure quality and safety of the additive (GMP certification)
Specific conditions for use in complementary feedingstuffs (if appropriate)	/

Maximum Residue Limit (MRL) (if appropriate)			
Marker residue	Species or category of animal	Target tissue(s) or food products	Maximum content in tissues
-	-	-	-

ASSESSMENT

This opinion is based in part on data provided by a single company involved in the production and distribution of L-tyrosine. It should be recognised that these data cover only a fraction of the existing additives containing L-tyrosine. The composition of the additives is not the subject of the application. The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has sought to use the data provided, together with data from other sources, to deliver an opinion.

1. Introduction

L-Tyrosine can be formed in the body from L-phenylalanine and is therefore a non-essential (dispensable) amino acid for protein synthesis in humans and animals. L-Tyrosine is also a precursor of the biosynthesis of melanin, which contributes to coat colour in many animal species.

The present application refers to L-tyrosine to be used as an amino acid for all animal species. L-Tyrosine is currently not authorised for use as an amino acid in the European Union. It has a dedicated monograph in the PhEur.⁹

L-Tyrosine is obtained by acid hydrolysis of natural keratin (poultry feathers).

2. Characterisation

2.1. Characterisation of the active substance/additive

L-Tyrosine (International Union of Pure and Applied Chemistry (IUPAC) name (2S)-2-amino-3-(4-hydroxyphenyl)propanoic acid, Chemical Abstracts Service (CAS) No 660-18-4) has a molecular weight of 181.2 g/mol; its molecular formula is $C_9H_{11}NO_3$ and its molecular structure is given in Figure 1.

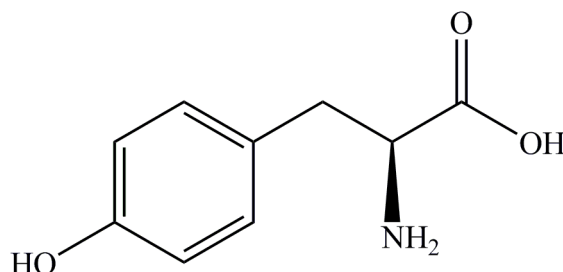


Figure 1: Molecular structure of L-tyrosine

The product contains, by specification, $\geq 95\%$ L-tyrosine. The specification is confirmed by the analysis of 71 batches, showing a mean of 96.7 % (range 95.1 to 98.2 %).¹⁰

2.2. Impurities

The absence of D-tyrosine was demonstrated by chiral chromatography. In the 71 batches mentioned above, the average moisture content was 0.2 %. Other impurities consisted of L-cystine, L-phenylalanine and sulphated ash, which with L-tyrosine and water constituted, on average, 99.9 % of the product. Average values for L-cystine, L-phenylalanine and ash were 0.5, 1.7 and 0.8 %, respectively. Heavy metals (lead, cadmium and mercury) and arsenic were analysed in four batches. The concentration of arsenic was < 0.04 mg/kg and the concentration of cadmium was < 0.03 mg/kg. The concentrations of lead (< 0.33 mg/kg) and mercury (≤ 0.3 mg/kg) were considerably higher.

⁹ European Pharmacopoeia, 7th edn, monograph 01/2008:1161.

¹⁰ Technical dossier/Section 2.1.3.

Microbiological analysis of five batches of L-tyrosine showed a range of aerobic plate counts of 110–11 000 colony-forming units (CFU)/g, while *Salmonella* was absent (in 100 g) and the counts of *Enterobacteriaceae*, coagulase-positive staphylococci, yeasts and moulds were consistently below the limits of detection.¹¹

2.3. Physical properties

The product is a beige/cream powder. Its density varies between 0.32 and 0.49 g/mL depending on the level of compaction. Its solubility in water is 0.45 g/L at 25 °C. Its melting point is 343 °C.

Particle size distribution was measured in four batches of the additive.¹² The mean particle size (laser diffraction) was approximately 6 µm (v/v), and up to 99.7 % of particles had dimensions < 150 µm. The dusting potential measured by a method based on the recommendations of EN 15051 in one batch of the additive was 42.7 mg/25 g.¹³ Although the results were not expressed in mg/m³, it is concluded that the product can be categorised as very dusty.

2.4. Manufacturing process

L-Tyrosine is obtained by acid hydrolysis of natural keratin (poultry feathers). The feathers are dissolved in 20 % HCl at 70 °C followed by hydrolysis at 106 °C. L-Tyrosine is eventually separated from L-cystine by crystallisation from alkaline solution.

2.5. Stability and homogeneity

2.5.1. Shelf-life

One study was performed by analysing 12 different batches of L-tyrosine stored for up to 48 months (three different batches per 12-month period) in plastic flasks at ambient temperature.¹⁴ The measured parameters were moisture, ash, L-tyrosine, L-cystine and L-phenylalanine. The data indicate no compositional changes after 48 months' storage.

A second study was performed in one batch of the additive stored in sealed polyethylene bags at 40 °C for six months.¹⁵ L-Tyrosine content, L-cystine, L-phenylalanine, drying losses and sulphated ash were monitored. Only minimal losses (< 0.5 %) of L-tyrosine were observed after six months.

2.5.2. Stability when used in premixtures and feedingstuffs

Stability studies in premixtures and feedingstuffs are based on a ring-trial validated Community method (Commission Regulation (EC) No 152/2009).¹⁶

The stability of the additive in a vitamins/minerals premixture for rabbits (supplemented at 2 %) was studied in three batches.¹⁷ The premixture was packed in paper bags (25 kg) lined with polyethylene film under ambient conditions for six months. No losses were detected.

The stability of the additive was tested in feedingstuffs for dogs and cats (dry and moist food), as well as chickens and piglets.

The stability of added L-tyrosine in dry pet food was measured in three studies using a total of 10 batches of dog and cat food (supplementation levels 0.34–0.43 %) for storage periods of up to 18

¹¹ Technical dossier/Section 2.1.4/Annex II/4.

¹² Technical dossier/Section II.2.1.5/Annex II.5.

¹³ Technical dossier/Section II.2.1.5/Annexes II.5 and II.6, and Section II.2.6.3.

¹⁴ Technical dossier/Section II.2.4.1.1/Annexes II.10 and 11.

¹⁵ Supplementary information (January 2012)/Annexes 1 and 2.

¹⁶ European Directive 152/2009 of 27 January 2009 laying down the methods of sampling and analysis for official control of feeds. OJ L 54, 26.02.2009, p. 130.

¹⁷ Supplementary information (January 2013)/Annex 10.

months. No losses of L-tyrosine were observed in any of the studies.^{18,19,20,21,22,23,24} Two moist pet foods (one canned for dogs and one in pouches for cats) were used to assess the stability of L-tyrosine (supplementation 0.125 % for the dog food, 0.13 % for the cat food) during food processing (sterilisation) and storage at 20 °C for three months. The dog food was based on rice, maize and chicken meat and that for cats was based on chicken and pig meat, salmon and wheat. Losses during food processing occurred only in the cat food (decrease of 6 % in free L-tyrosine content). Losses during food storage were observed only in the dog food (up to 5 % in free L-tyrosine content).^{25,26}

The stability of one batch of L-tyrosine was also studied in feeds for chickens for fattening and piglets. The basal diets (intended supplementation 0.25 % L-tyrosine) were mainly composed of wheat, maize and soybean meal. Pelleting (75 °C for the chicken diet and 65 °C for the piglet diet) resulted in a 4 % loss of free L-tyrosine only in piglet feed. After three months of storage of both complete feeds at 20 °C, no losses of free L-tyrosine were observed.^{27,28}

2.5.3. Homogeneity

Ten subsamples of a premixture for rabbits were taken during production and analysed for free L-tyrosine. The coefficient of variation (CV) of the mean was 4 %.²⁹

The homogeneous distribution of the extruded pet foods for cats and dogs was analysed after mixing, extrusion (including drying) and final coating. From the pet food produced, 13 samples were taken before extrusion and 20 were taken after extrusion. The CVs ranged from 1 to 4 %.³⁰

From two canned final foods for dogs and cats, 10 subsamples each were taken. The CV of the free L-tyrosine concentration was 4 % in both cases.^{31,32}

Another 10 subsamples each were taken from the pelleted feed for chickens for fattening and piglets. The CV of the free L-tyrosine concentration was 5 % in both cases.^{33,34}

2.6. Conditions of use

L-Tyrosine is intended to be used in feed and food for all animal species and categories. According to the applicant, the maximum recommended supplementation levels vary from 0.5 % (food-producing animals) to 1.5 % (non-food-producing animals).³⁵ The product can be added directly to complete or complementary feedingstuffs.

To obtain desirable hair colouring, the applicant recommends a minimum total concentration of the sum of L-tyrosine and L-phenylalanine of 1.8 and 1.9 % in dry foods for cats and dogs, respectively.³⁶

¹⁸ Technical dossier/Section II.4.1.2.A1/Annex II.12.

¹⁹ Technical dossier/Section II.4.1.2.A2/Annex II.12.

²⁰ Supplementary information (January 2013).

²¹ Supplementary information (January 2012)/Qiii.

²² Technical dossier/Section II.4.1.2.A2/Annex II.12.

²³ Supplementary information (January 2013).

²⁴ Supplementary information (January 2012).

²⁵ Supplementary information (January 2013)/Annex 1.

²⁶ Supplementary information (January 2013)/Annex 2.

²⁷ Supplementary information (January 2013)/Annex 8.

²⁸ Supplementary information (January 2013)/Annex 9.

²⁹ Supplementary information (January 2013)/Annex 10.

³⁰ Technical dossier/section II.2.4.2/Annex II.12.

³¹ Supplementary information (January 2013)/Annex 1.

³² Supplementary information (January 2013)/Annex 2.

³³ Supplementary information (January 2013)/Annex 8.

³⁴ Supplementary information (January 2013)/Annex 9.

³⁵ Supplementary information (April 2013).

³⁶ Supplementary information (January 2012).

2.7. Evaluation of the analytical methods by the European Union Reference Laboratory (EURL)

EFSA has verified the EURL report as it relates to the methods used for the control of L-tyrosine in animal feed. The Executive Summary of the EURL report can be found in Appendix A.

3. Safety

L-Tyrosine is usually absorbed in the proximal small intestine. Any L-tyrosine reaching the large intestine is decarboxylated to tyramine, a biogenic amine, in the human gut. Inadequate degradation (detoxification) of formed tyramine by the gut monoamine oxidases can lead to tyramine entering the systemic circulation. Tyramine acts as a vasopressor (Broadly et al., 2009; Marcobal et al., 2012); it is known to be a cause of migraine headaches in humans (D'Andrea et al., 2012). Very recently, for a single oral administration in healthy individuals, a no observed adverse effect level (NOAEL) of 200 mg tyramine/person has been proposed, based on a literature survey (Paulsen et al., 2012). In contrast, individuals with reduced monoamine oxidase activity may suffer hypertension after ingestion of < 5 mg tyramine (Davey and Farmer, 1963). Intellectual deficit problems seem to occur when human neonates receive abnormally high quantities of L-tyrosine (Mamunes et al., 1976).

3.1. Safety for the target species

Tolerance studies are not required for amino acids naturally occurring in the proteins of animals or plants already authorised as feed additives (Regulation (EC) No 429/2008). The FEEDAP Panel considers that this is also applicable to other amino acids naturally occurring in the proteins of plants and animals.

If the dietary concentrations proposed in the conditions of use (up to 1.5 % L-tyrosine in pet animals) are exceeded, the potential microbial synthesis of tyramine in the foregut of the ruminants and hindgut of all animals showing a significant microbial load in the gastrointestinal tract should not be dismissed. Tyramine may be produced by a variety of Gram-positive bacteria, including lactobacilli and enterococci, and by Gram-negative bacteria (Nugon-Baudon et al., 1985a, b; Dierick et al., 1986; Shalaby, 1996; Marcobal et al., 2012). Inadequate degradation (detoxification) of tyramine may cause adverse effects (Nugon-Baudon et al., 1985a, b; Shalaby, 1996; Pietzak et al., 2002). In a 42-day oral toxicity study (Til et al., 1997) with Wistar rats (levels of tyramine: 0, 200, 2 000 or 10 000 mg/kg feed), the NOAEL (end points: reduced body weight and plasma alkaline phosphatase, increased liver weight) was set by the authors at 2 000 mg/kg feed (180 mg/kg body weight (bw)/day).

Young rats fed a low-protein diet containing 3 % tyrosine developed eye and paw lesions and their growth was retarded (Alam et al., 1966). Rats receiving 5 % dietary tyrosine developed eye lesions within a few days (Rich et al., 1973); in the same study, the addition of 10 % tyrosine led to death within 10 days. In pregnant rats, the administration of 500 mg/kg bw caused subsequent behavioural problems in offspring, but 20 mg/kg bw did not (Arevalo et al., 1987).

Few examples of toxicity to farm livestock or non-food-producing animals were found. In a study with male White Leghorn chickens, the addition of 5 % tyrosine to a basal diet (20 % crude protein) resulted in a depression of feed intake, reduced body weight gain, nitrogen and energy retention, and impaired feed efficiency; the growth retardation was the result not only of the reduced feed intake, but also of a reduced efficiency of feed utilisation (Yanaka and Okumura, 1982). In growing turkeys fed a low-protein diet (180 g crude protein/kg), dietary supplementation with 6.7 g tyrosine/kg of feed (analysed total tyrosine 9.7 g/kg of feed) led to slightly reduced feather weight but no other detrimental effects (Wylie et al., 2003).

It was demonstrated that the manufacturing process was very efficient in inactivating viruses.³⁷ A second study concluded that there was no risk of transmission of avian viruses³⁸.

3.1.1. Conclusions on the safety for target species

L-Tyrosine is considered safe for all animal species provided the conditions of use are respected, i.e. supplementation of conventional diets with 0.5 % L-tyrosine for food-producing animals and 1.5 % for non-food-producing species. Higher dietary concentrations may lead to growth rate depression and eye lesions, and, in young animals, behavioural alterations.

3.2. Safety for the consumer

L-Tyrosine will be incorporated in the body protein of the animal. The protein composition will not be changed. Free L-tyrosine will not be stored in the tissues. No risk is expected for the consumer from the use of this L-tyrosine preparation showing a purity > 95 % as a feed additive.

The Joint FAO/WHO expert committee of Food Additives (JECFA, 2005) assessed L-tyrosine when used as a flavouring and found no safety concerns.

3.3. Safety for the user

Since the product is a fine powder, the possibility of respiratory exposure is high. In the absence of experimental data, inhalation toxicity cannot be ruled out. No studies were provided on the effects of the additive on eyes or skin. In the absence of such data, this product should be considered as an irritant to the skin and eyes and as a skin sensitiser.

3.4. Safety for the environment

L-Tyrosine is a physiological and natural component of animals and plants. It is not excreted as such, but as urea, uric acid, CO₂, catecholamines (Agharanya et al., 1981) and occasionally as homogentisic acid (Sealock and Silberstein, 1940). All these compounds, with the exception of CO₂, would be degraded rapidly by environmental microbes. The use of L-tyrosine in animal nutrition would not be expected to lead to any localised increase in the concentration in the environment. It is concluded that the use of this product as a feed additive does not represent a risk to the environment.

4. Efficacy

L-Tyrosine is considered to be a conditionally essential amino acid. It can be synthesised from L-phenylalanine, which is an essential amino acid. If insufficient L-phenylalanine is available, L-tyrosine then becomes essential. Therefore, if L-phenylalanine is present in sufficient quantity in the diet, L-tyrosine is non-essential, which is the normal circumstance. If the conversion of L-phenylalanine to L-tyrosine is compromised, as in phenylketonuria, or in very young humans, in whom the demand for L-phenylalanine is exceptionally high, additional dietary L-tyrosine may be required for protein synthesis and growth.

In most animal species, L-tyrosine can satisfy about 50 % of the total requirements for two aromatic amino acids: L-phenylalanine and L-tyrosine (e.g. Sasse and Baker, 1972; Robbins and Baker, 1977; Anderson et al., 1980; National Research Council (NRC), 1998). Dietary L-phenylalanine and L-tyrosine requirements, as a percentage of complete feed, are in the range 1.06–1.25 for piglets (5–20 kg bw), 0.55–0.87 for grower/finisher pigs, 0.48–0.54 for pregnant sows, 0.75–1.14 for lactating sows, 0.69–1.04 for laying hens, 1.04–1.34 for chickens for fattening, 0.8–1.8 for turkeys and are around 1.04 for growing dogs, 0.59 for adult dogs and 1.53 for growing cats (Leilis and Speer 1985; Speer et al., 1990; NRC, 1994, 1998, 2006). L-Tyrosine and L-phenylalanine are among the most abundant amino acids in cereal-/soybean-based diets (about 1.4 % L-phenylalanine + L-tyrosine; NRC, 1998). Animal products—except gelatine, which is deficient in L-phenylalanine and L-tyrosine

³⁷ Technical dossier/Section III/Annex III.1.

³⁸ Technical dossier/Section III/Annex III.2.

(approximately 2.5 g L-phenylalanine + L-tyrosine/16 g N)—also contain high concentrations of the aromatic amino acids. Deficiencies are therefore unlikely to occur under practical feeding conditions. There is therefore no practical need for L-tyrosine in food-producing animals, as a sufficient amount is usually present in common dietary constituents (Appendix B).

Besides their role as a constituent of proteins, aromatic amino acids also act as precursors of neurotransmitter catecholamines (e.g. L-DOPA, dopamine, adrenaline). The metabolism of L-phenylalanine and L-tyrosine is shown in Figure C1 in Appendix C. In humans, the function of L-tyrosine as a precursor to catecholamines has been reviewed by EFSA (EFSA, 2011) in view of possible benefits for mental performance. The NDA Panel concluded that a cause and effect relationship had been established between the consumption of L-tyrosine in a protein-adequate diet and contribution to normal synthesis of catecholamines. However, no evidence had been provided that the protein supply in the diet of the European human population was not sufficient to fulfil this function of the amino acid. Experiments reported by Hammerl and Rüsse (1987a, b) and Hammerl and Müller (1988) indicated that L-tyrosine application may improve the reproductive performance of rats and sows. L-Tyrosine appeared to reduce the post-weaning interval to conception and increase litter size in rats and gilts by stimulating catecholamine synthesis. However, these results were not confirmed by a more recent study with a large number of sows receiving basal diets containing 0.51–0.56 % L-tyrosine and 0.68–0.72 % L-phenylalanine, and an additional 100 mg L-tyrosine/kg bw (Rettmer et al., 1993). Rettmer et al. (1993) cited other studies in which no similar response had been observed, and concluded that the diets used by the Hammerl group had possibly been unusually limiting in L-tyrosine.

Another route of L-tyrosine metabolism is the synthesis of the pigment melanin (Figure C1, Appendix C). For this reason, L-tyrosine may have a desirable effect in non-food-producing animals, specifically in cases where intensive colouring is required as for fur production, or for pigmentation of the skin or coat. Based on studies of one research group (Anderson et al., 2002; Morris et al., 2002) and findings in breeding colonies, it was concluded that the L-tyrosine (+ L-phenylalanine) requirements of black-coated cats and dogs are higher because of the need to develop and maintain optimum fur colour. Morris et al. (2002) presented several experiments with a small number of young cats (one to four animals per treatment group) fed semi-purified diets containing graded levels of L-phenylalanine and L-tyrosine. The authors concluded that the requirement for the maintenance of black hair colour is in the range of 1.8 to 2.4 % of the diet, which would be more than twice the requirement for maximal growth as proposed by the older NRC edition (0.9 % phenylalanine + tyrosine; NRC, 1986). In another series of studies with black cats fed purified diets containing graded concentrations of L-phenylalanine and L-tyrosine (0.6–2.4 %) and different phenylalanine–tyrosine ratios, a linear relationship between plasma L-tyrosine and pyrrole-2,3,5-tricarboxylic acid in the hair (an oxidation product of eumelanin) could be observed; the inflection point occurred at about 1.6 % phenylalanine + tyrosine/kg diet (Anderson et al., 2002). Moreover, cats receiving less than 1.6 % aromatic amino acids in the diet developed reddish hairs. Based on these studies, the authors recommended a dietary concentration of ≥ 1.8 % phenylalanine + tyrosine.

The applicant also submitted three publications on Chinese Taihe silky fowls (Li et al., 2003, 2008; Zhang et al., 2010).³⁹ Li et al. (2003) showed that the amino acids requirement of growing Taihe silky fowls was in the range of growing pullets and chickens for fattening. Li et al. (2008) concluded that the growth performance and melanin content in muscle tissue and plumage of Taihe silky fowls could be improved by controlling the dietary L-tyrosine, L-phenylalanine and L-tryptophan to the appropriate levels and ratios (0.8 % L-tyrosine and 1.1 % L-phenylalanine). Zhang et al. (2010) reported only zootechnical and biochemical parameters as affected by L-phenylalanine and L-tyrosine. However, Li et al. (2009) found that the increase in melanin in pectoral muscle and skin could be achieved with L-phenylalanine supplementation alone.

³⁹ Supplementary information (January 2013)/Annexes 5, 6 and 7.

4.1. Conclusion on efficacy for all species

The supplementation of feed with L-tyrosine, a non-essential amino acid, is efficacious in cases where high requirements for tyrosine as a melanin precursor occur or where the sum of L-phenylalanine and L-tyrosine does not meet growth requirements. The benefit to coat colour has been demonstrated for cats. L-Tyrosine may also have the potential to intensify the pigmentation of the coat/plumage of other species, but limited evidence is available.

5. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan, other than those established in the Feed Hygiene Regulation⁴⁰ and Good Manufacturing Practice.

CONCLUSIONS

L-Tyrosine is considered safe for all animal species, provided that the conditions of use are respected, i.e. supplementation of conventional diets with 0.5 % L-tyrosine for food-producing animals and 1.5 % for non-food-producing species. Higher dietary concentrations may lead to growth rate depression and eye lesions, and, in young animals, behavioural changes.

L-Tyrosine will be incorporated in the body protein of the animal without affecting its protein composition. Free L-tyrosine will not be stored in the tissues. The FEEDAP Panel concludes that use of L-tyrosine with a purity > 95 % as a feed additive is safe for consumers.

In the absence of data, the product is considered potentially irritating to skin and eyes, a potential dermal sensitiser and hazardous by inhalation.

The use of L-tyrosine in animal nutrition would not be expected to lead to any localised increase in the concentration of L-tyrosine or its metabolites in the environment. It is concluded that the use of this product as a feed additive does not represent a risk to the environment.

The supplementation of feed with L-tyrosine is efficacious in cases where high requirements for L-tyrosine as a melanin precursor occur or where the sum of L-phenylalanine and L-tyrosine does not meet growth requirements. The benefit to coat colour has been demonstrated for cats. L-Tyrosine may also have the potential to intensify the pigmentation of the coat/plumage of other species, but limited evidence is available.

DOCUMENTATION PROVIDED TO EFSA

1. FAD-2010-0260. November 2010. Submitted by Bretagne Chimie Fine.
2. FAD-2010-0260. Supplementary information. January 2012. Submitted by Bretagne Chimie Fine.
3. FAD-2010-0260. Supplementary information. January 2013. Submitted by Bretagne Chimie Fine.
4. Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for L-tyrosine.

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APPENDICES

Appendix A.

Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Methods of Analysis for L-tyrosine⁴¹

In the current application authorisation is sought for *L-Tyrosine* under Articles 4(1), category ‘nutritional additives’ and functional group 3(c) ‘amino acids, their salts and analogues’ according to Annex I of Regulation (EC) No 1831/2003. Specifically, authorisation is sought for the use of *L-Tyrosine* for all animal species and categories. The *feed additive* is intended to be mixed either in *premixtures* or added directly to complete *feedingstuffs*. The Applicant suggested no minimum or maximum *L-Tyrosine* concentrations in *premixtures* and *feedingstuffs*.

For the determination of the *active substance* in the *feed additive* the Applicant submitted a single laboratory validated and further verified method based on UV-visible spectrophotometry. Nevertheless, the EURL suggests the internationally recognised European Pharmacopoeia titrimetric method for which no performance characteristics are provided. However, the EURL considers this method suitable to determine *L-Tyrosine* in the *feed additive* within the frame of official control.

For the determination of *Tyrosine* in *premixtures* and *feedingstuffs* the Applicant submitted the ring-trial validated Community method (Commission Regulation (EC) No 152/2009). The method applies for the determination of *free* (synthetic and natural) and *total* (peptide-bound and free) amino acids, using an amino acid analyser or High Performance Liquid Chromatography (HPLC) equipment. The performance characteristics reported for a variety of amino acids are:

- a relative standard deviation for *repeatability* (RSD_r) ranging from 0.9 to 7.0 %;
- a relative standard deviation for *reproducibility* (RSD_R) ranging from 4.1 to 23.3 %.

Based on the performance characteristics presented, the EURL recommends for official control, the ring-trial validated Community method based on ion exchange chromatography coupled with post-column derivatisation and photometric detection to determine *Tyrosine* in *premixtures* and *feedingstuffs*.

Further testing or validation of the methods to be performed through the consortium of National Reference Laboratories as specified by Article 10 (Commission Regulation (EC) No 378/2005) is not considered necessary.

⁴¹ The full report is available on the EURL website: <http://irmm.jrc.ec.europa.eu/SiteCollectionDocuments/FinRep-FAD-2010-0260.pdf>

Appendix B.

Concentration of L-phenylalanine and L-tyrosine in comparison to L-lysine in common feed ingredients. Data for plant products from NRC (1998)

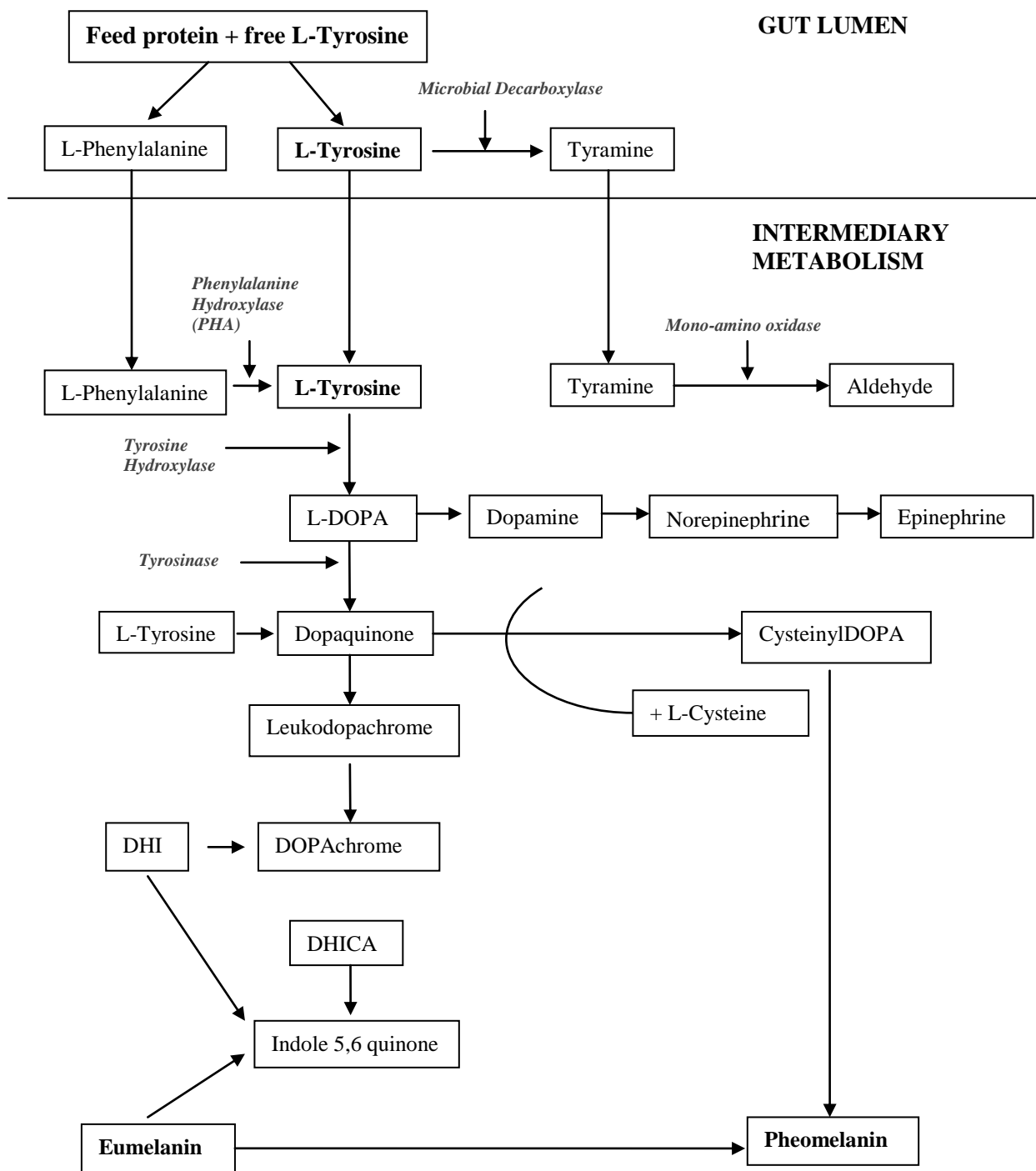
	CP (%)	L-Lysine		L-Phenylalanine		L-Tyrosine	
		%	g/16 g N	%	g/16 g N	%	g/16 g N
Alfalfa	19.6	0.90	4.6	0.93	4.7	0.60	3.1
Barley	10.5	0.36	3.4	0.49	4.7	0.32	3.1
Maize	8.3	0.26	3.1	0.39	4.7	0.25	3.0
Rice	7.9	0.30	3.8	0.39	4.9	0.38	4.8
Wheat	11.5	0.38	3.3	0.63	5.5	0.37	3.2
Maize gluten feed	21.5	0.63	2.9	0.76	3.5	0.58	2.7
Soybean meal	43.8	2.83	6.5	2.18	5.0	1.69	3.9
Soy protein concentrate	64.0	4.20	6.6	3.40	5.3	2.50	3.9
Fish meal	64.6	5.11	7.9	2.66	4.1	2.15	3.3
Liver meal	62.0	4.34	7.0	2.08	3.4	2.22	3.6
Meat meal	54.0	3.07	5.7	2.17	4.0	1.40	2.6
Poultry meal	64.1	3.32	5.2	2.26	3.5	1.56	2.4
Whey powder	12.1	0.90	7.4	0.36	3.0	0.25	2.1
Plasma protein	80.0	6.80	8.5	4.60	5.8	3.60	4.5
Gelatine	87.6	3.55	4.0	1.71	1.9	0.47	0.5

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Appendix C.

Metabolic fate of L-tyrosine



Legend: DHI = 5,6-dihydroxyindole; DHICA = 5,6-dihydroxyindole-2-carboxylic acid

Figure C1: Fate of tyrosine: formation of catecholamine neurotransmitters and melanin biosynthesis (adapted from Tobin, 2008)

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