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Safety and efficacy of inositol as nutritional additive for dogs and cats

EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP)

Abstract

Inositol (cyclohexenehexol) is a sugar alcohol synthesised by most plants and animals. It exists in nine possible stereoisomers, four of which are physiologically active. Inositol is an essential micronutrient for salmon, carp, tilapia and shrimps, particularly juveniles. In a previous opinion on inositol, the EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP6) could not conclude on the safety and efficacy of inositol when used in pet food at the recommended use levels of between 500 and 3,000 mg/kg owing to insufficient evidence. The European Commission requested that the European Food Safety Authority re-evaluate the safety and efficacy of inositol when used as nutritional additive (functional group: vitamins, pro-vitamins and chemically well-defined substances having a similar effect) in food for dogs and cats. In the present application, the applicant proposed a maximum supplementation level of 1,500 mg inositol/kg dry complete feed for dogs and cats. The FEEDAP Panel concluded, based on the free inositol concentrations found in commercial diets for pets, that inositol up to a total content of 3,000 mg free inositol/kg dry complete feed (88% dry matter) could be considered safe for dogs and cats. Evidence is lacking for any benefit of inositol supplementation of foods for dogs and cats.

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Keywords: inositol, nutritional additive, safety, efficacy, cats, dogs

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Summary

Inositol, a carbocyclic polyol, is a sugar-like carbohydrate synthesised by most plants and animals. It exists in nine possible stereoisomers, four of which are physiologically active. Inositol is an essential micronutrient for salmon, carp, tilapia and shrimps, particularly juveniles.

In 2014, the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) delivered an opinion on inositol when used as nutritional additive (functional group: vitamins, pro-vitamins and chemically well-defined substances having a similar effect) for fish, cats and dogs at the recommended use levels of between 250 and 500 mg/kg feed for fish and 500 and 3,000 mg/kg for cats and dogs (EFSA FEEDAP Panel, 2014). The safety of the additive for fish and crustaceans, consumers, users of the additive (if protective measures recommended in Regulation (EU) No 1249/2014 are used) and the environment was established at that time. However, based on the study provided in dogs, it was not possible to (i) demonstrate the essentiality of dietary inositol for dogs and (ii) conclude on the safety of dietary inositol at the recommended supplementation levels of between 500 and 3,000 mg/kg. The FEEDAP Panel was not in a position to conclude on the efficacy and safety of inositol for cats.

In the present application, the applicant proposed supplementation levels of 1,100–1,500 mg/kg dry complete feed for dogs and cats.

Inositol is a natural metabolite that is converted primarily to innocuous cellular compounds and does not have the potential to accumulate. No specific tolerance or toxicity studies were available for cats and dogs. Exposure of target animals to inositol when consuming dry complete feed supplemented with inositol is no more than when consuming wet complete feeds. Thus it can be concluded that inositol up to a total content of 3,000 mg free inositol/kg dry complete feed (88% dry matter) could be considered safe for dogs and cats.

Inositol has been shown *in vivo* to have an effect on the efficacy of the skin barrier but only in combination with vitamins and other vitamin-like substances. Otherwise, evidence is lacking for any benefit of inositol supplementation of foods for cats and dogs.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003¹ establishes rules governing the Community authorisation of additives for use in animal nutrition and, in particular, Article 9 defines the terms of the authorisation by the Commission.

The applicant Intertek Scientific & Regulatory Consultancy acting on behalf of Royal Canin² is seeking a Community authorisation of inositol to be used as a nutritional additive for cats and dogs (Table 1).

Table 1: Description of the substance

Category of additive	Nutritional additives
Functional group of additive	Vitamins, pro-vitamins and chemically well-defined substances having a similar effect
Description	Inositol Maximum levels of 1,100–1,500 mg/kg
Target animal category	Cats and dogs
Applicant	Intertek Scientific & Regulatory Consultancy acting on behalf of Royal Canin
Type of request	New opinion

On 9 April 2014,³ the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) of the European Food Safety Authority ('Authority'), in its opinion on the safety and efficacy of the product (EFSA FEEDAP Panel, 2014), with respect to cats and dogs stated that:

'Based on the study in dogs it was not possible to (i) demonstrate the essentiality of dietary inositol for dogs and (ii) conclude on the safety of dietary inositol at the recommended use levels of between 500 and 3,000 mg/kg. The FEEDAP Panel is not in a position to conclude on the efficacy and safety of inositol for cats.'

The Commission gave the possibility to the applicant to submit complementary information in order to complete the assessment on the safety and the efficacy of the product to allow a revision of the Authority's opinion.

The applicant has assembled a new set of supplementary data and information to address the gaps identified by the FEEDAP.⁴ The applicant recommends a typical supplementation rate of 1,100 mg/kg dry pet food up to a maximum of 1,500 mg/kg dry pet food (88% dry matter).

In view of the above, the Commission asks the Authority to issue a new opinion on the safety and efficacy of inositol as a nutritional additive for cats and dogs based on the additional data submitted by the applicant and the proposed levels.

1.2. Additional information

Inositol (cyclohexanehexol) is a carbocyclic polyol, a sugar alcohol, synthesised by most plants and animals. It exists in nine possible stereoisomers, four of which are physiologically active (EFSA FEEDAP Panel, 2014). Inositol is an essential micronutrient for salmon (Waagbø et al., 1998), carp (Jiang et al., 2009), tilapia (Shiau and Su, 2005) and shrimps (Shiau and Su, 2004), particularly juveniles. In contrast to animal products, in plant products, inositol is present in a bound form as phytic acid, which is not bioavailable unless the diet contains enough endogenous or exogenous phytase.

In 2014, the European Food Safety Authority (EFSA) was requested by the European Commission to re-evaluate inositol when used as nutritional additive (functional group: vitamins, pro-vitamins and

¹ 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.

² The Commission received a dossier from the applicant Vitamin Authorization Consortia European Economic Interest Group (VITAC EEIG), requesting an authorisation of Inositol to be used as a nutritional additive for fish, cats and dogs. On 30 April 2015, the Commission was informed that as of 30.4.2015, the company responsible for the application of Inositol as a feed additive (FAD-2010-0196) is Intertek Scientific & Regulatory Consultancy acting on behalf of Royal Canin.

³ http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3671.pdf

⁴ Dossier reference: FAD-2015-0021.

chemically well-defined substances having a similar effect) for fish, cats and dogs at the recommended use levels of between 250 and 500 mg/kg feed for fish and 500 and 3,000 mg/kg feed for dogs and cats (EFSA FEEDAP Panel, 2014). The safety of the additive for fish and crustaceans, consumers, users and the environment was established at that time. However, based on the study provided in dogs, it was not possible to (i) demonstrate the essentiality of dietary inositol for dogs and (ii) conclude on the safety of dietary inositol at the recommended supplementation levels of between 500 and 3,000 mg/kg. The FEEDAP Panel was not in a position to conclude on the efficacy and safety of inositol for cats.

Inositol is currently authorised for use in fish and crustaceans (Regulation (EU) No 1249/2014⁵).

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of additional information⁴ to a previous application on the same product.⁶

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of inositol is in line with the principles laid down in Regulation (EC) No 429/2008⁷ and the relevant guidance documents: Guidance on nutritional additives (EFSA FEEDAP Panel, 2012), Technical guidance: Tolerance and efficacy studies in target animals (EFSA FEEDAP Panel, 2011a), Guidance on the assessment of additives intended to be used in pets and other non food-producing animals (EFSA FEEDAP Panel, 2011b).

3. Assessment

General information on absorption, distribution, metabolism and excretion (ADME), as well on the toxicology were described in the previous EFSA opinion on inositol (EFSA FEEDAP Panel, 2014). The ADME properties of inositol did not raise safety concerns (EFSA FEEDAP Panel, 2014). Inositol is an endogenous metabolite that is converted primarily to innocuous cellular compounds and does not have the potential to accumulate. Inositol has a low oral toxicity in rodents and humans.

In the previous opinion it was not possible to conclude on the safety and efficacy for cats and dogs. The applicant intends to use inositol at a typical supplementation rate of 1,100 mg/kg dry complete feed up to a maximum of 1,500 mg/kg dry complete feed (88% dry matter) for dogs and cats.⁸

3.1. Safety for dogs and cats

The FEEDAP Panel (EFSA FEEDAP Panel, 2014) could not conclude on the safety of dietary inositol for dogs at the recommended use levels between 500 and 3,000 mg/kg. The FEEDAP Panel also could not conclude on the safety of inositol for cats. The applicant, however, has reduced the maximum dose to 1,500 mg/kg dry complete feed for dogs and cats and this is the maximum supplementation level considered in the current safety assessment.

3.1.1. Exposure assessment⁹

3.1.1.1. Concentration in feed materials

Inositol is naturally present in plant and animal tissues, including a number of common feed materials that are components of dog and cat food. In contrast to animal products, in plant products, most of the inositol is present in a bound form as phytic acid, which is not bioavailable unless the diet contains enough endogenous or exogenous phytase (Pallauf and Rimbach, 1997).

⁵ Commission Regulation (EU) No 1249/2014 of 21 November 2014 concerning the authorisation of inositol as a feed additive for fish and crustaceans. OJ L 335, 22.11.2014, p. 3.

⁶ Dossier reference: FAD-2010-0196.

⁷ Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

⁸ Technical dossier/Section III.3.1.

⁹ This section has been amended following the applicable provisions on confidentiality.

Analyses of the free (bioavailable) inositol content of typical feed materials used in the production of compound feed for dogs and cats was conducted by gas chromatography (GC) (no hydrolysis step applied) and the results are presented in Table 2.¹⁰ The natural free inositol content of the feed materials analysed ranged from below limit of quantification (LOQ, 100 mg/kg) to 3,800 mg/kg on an as-is basis (< LOQ to about 13,000 mg/kg on dry matter basis). In particular, feed materials high in animal protein generally contained higher levels of inositol than grain- or cereal-based ingredients (i.e. corn, brewer's rice, wheat gluten).

Table 2: Inositol content of some feed materials used in dog and cat food (data from the applicant)

Food category	Feed material	Dry matter (%)	Inositol (mg/kg) ^(a)	
			Fresh weight basis	Dry weight basis ^(b)
Dried animal protein	Dehydrated poultry protein	96.0	3,100–3,800	3,229–3,958
	Dehydrated pork protein	97.0	200	206
	Hydrolysed animal protein	96.6	1,900–2,000	1,967–2,174
Animal fat	Poultry fat	99.9	< LOQ	< LOQ
Organs and meat	Pork liver	28.5	300	1,053
	Pork kidney	20.0	800–1,000	4,000–5,000
	Chicken and mechanically deboned meat	37.5	500–600	1,333–1,600
	Chicken skin	50.0	500–600	1,000–1,200
	Chicken liver and heart	24.0	2,200–3,100	9,167–12,917
	Chicken viscera	27.0	1,200–1,300	4,444–4,815
Cereals	Maize	87.4	200–300	229–343
	Brewers' rice	85.8	< LOQ–200	< LOQ–233
Vegetal protein	Wheat gluten	93.9	300	319

LOQ: limit of quantification, 100 mg/kg.

(a): Measured by gas chromatography. No hydrolysis step was used.

(b): Inositol on dry matter basis was calculated as inositol content on a fresh weight basis/percentage of dry matter.

3.1.1.2. Estimated inositol exposure due to supplementation in complete feed for dogs and cats

The applicant measured the free inositol content of 17 samples of commercial complete feed for dogs (4 wet and 6 dry, 2 of the dry were supplemented with inositol at 1,100–1,500 mg/kg complete feed) and cats (3 wet and 4 dry, 2 of the dry were supplemented with inositol as mentioned above).¹¹ The results are shown in Table 3.

Table 3: Analysed content of free (bioavailable) inositol in commercial complete feeds for dogs and cats (composition of the diets were not described)

Species	Diet	Kind of food	Inositol addition ^(a)	Free inositol (mg/kg food 'as is') ^(b)	Moisture (%)	ME (kJ/kg food as is)	mg of inositol/kJ ME
Adult dog	A	Dry	No	1,000–1,100	9.5	16,689	0.060–0.066
	B	Dry	No	900–1,100	9.5	16,534	0.054–0.067
	C	Dry	No	400–600	9.5	15,739	0.025–0.038
	D	Dry	Yes	1,600–1,900	9.5	16,283	0.098–0.117
	E	Wet	No	300–400	74.5	4,939	0.061–0.081
	F	Wet	No	600–700	70	5,357	0.112–0.131
Adult cat	G	Dry	No	1,100–1,300	5.5	14,274	0.077–0.091
	H	Dry	Yes	1,900–2,200	5.5	16,073	0.118–0.137
	I	Wet	No	500–600	79	3,457	0.145–0.174
	J	Wet	No	500–600	78.5	3,767	0.133–0.159

¹⁰ Technical dossier/Supplementary information April 2016/EFSA-Q-2015-00367 Supplementary information inositol for cats and dogs.

¹¹ Technical dossier/Supplementary information April 2016/EFSA-2015-00367 Supplementary information inositol for cats and dogs.

Species	Diet	Kind of food	Inositol addition ^(a)	Free inositol (mg/kg food 'as is') ^(b)	Moisture (%)	ME (kJ/kg food as is)	mg of inositol/kJ ME
Growing dog	K	Dry	No	800–900	9.5	15,906	0.050–0.057
	L	Dry	Yes	1,700–2,000	9.5	17,120	0.099–0.117
	M	Wet	No	400–500	78.0	4,395	0.091–0.114
	N	Wet	No	400–500	78.0	4,374	0.091–0.114
Growing cat	O	Dry	No	900–1,000	5.5	16,241	0.055–0.062
	P	Dry	Yes	2,000–2,100	5.5	16,994	0.118–0.124
	Q	Wet	No	500–600	78.0	4,102	0.122–0.146

ME: metabolisable energy.

(a): Inositol was incorporated at 1,100–1,500 mg/kg dry complete feed.

(b): Measured by gas chromatography. No hydrolysis step was used.

Food intake in dogs and cats is governed principally by the energy content of the diet. Comparing the inositol content per unit of metabolisable energy (mg inositol/kJ ME) in commercial supplemented dry complete feed of dogs or cats with that of commercial non supplemented wet complete feed of dogs and cats (Table 3), the supplemented dry complete feed contains in general similar (dog diets) or a bit less (cat diets) free inositol than the non-supplemented wet complete feed.

3.1.2. Animal studies

The applicant submitted two studies in dogs. One of them was not further considered because of the short duration (2 weeks) and the low doses tested.¹² The second study, although of 1 year duration, could not be considered because it was conducted with diabetic mongrel dogs and exposure to total inositol could not be extracted from the study.¹³

No new information was available on the tolerance of cats to inositol.

3.1.2.1. Conclusions on safety for the target species

Based on the inositol concentrations found in commercial diets for pets, the FEEDAP Panel concludes that inositol up to a total content of 3,000 mg free inositol/kg dry complete feed could be considered safe for dogs and cats. In general, this would allow supplementing dry diets for cats and dogs with up to 1,500 mg inositol/kg dry complete feed.¹⁴

3.2. Efficacy for dogs and cats

The FEEDAP Panel concluded in its previous assessment (EFSA FEEDAP Panel, 2014) that based on the study provided in dogs (Watson et al., 2006), where inositol was supplemented in combination with other nutrients, it was not possible to demonstrate the essentiality of dietary inositol alone for dogs. Similarly, the FEEDAP Panel was not in a position to conclude on the efficacy of inositol for cats.

In the new set of information, the applicant provided a historical study on the effects of inositol in preventing and treating alopecia in rats (Cunha et al., 1943). The study was considered not relevant to the assessment of the efficacy of inositol in dogs and cats. No more data were available. The FEEDAP Panel found no reason to change its previous conclusion.

4. Conclusions

Based on the inositol concentrations found in some commercial diets for pets, the FEEDAP Panel concludes that inositol up to a total content of 3,000 mg free inositol/kg complete dry feed could be considered as safe for dogs and cats. In general, this would allow supplementing dry diets for cats and dogs with up to 1,500 mg inositol/kg dry complete feed.

Based on the submitted data, the FEEDAP Panel is not in a position to conclude on the efficacy of inositol for dogs and cats.

¹² Technical dossier/References section III/III.15. Unpublished (2011).

¹³ Technical dossier/References section III/III.1 Al-Adli et al. (1993).

¹⁴ Dry diet is considered containing 88% dry matter.

Documentation provided to EFSA

- 1) Inositol for cats and dogs. June 2015. Submitted by Intertek Scientific & Regulatory Consultancy acting on behalf of Royal Canin.
- 2) Inositol for cats and dogs. Supplementary information April 2016. Submitted by Intertek Scientific & Regulatory Consultancy acting on behalf of Royal Canin.

References

- Al-Adli N, Torres R, Baker H, Patel J, Abdel-Sayed M and Regan T, 1993. Influence of dietary myoinositol on myocardial vulnerability and norepinephrine release in a diabetic animal model. *International Journal of Cardiology*, 42, 21–29.
- Cunha TJ, Kirkwood S, Phillips PH and Bohstedt G, 1943. Effect of inositol upon rat alopecia. *Experimental Biology and Medicine (Maywood)*, 54, 236–238.
- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011a. Technical guidance: Tolerance and efficacy studies in target animals. *EFSA Journal* 2011;9(5):2175, 15 pp. doi:10.2903/j.efsa.2011.2175
- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2011b, revised in 2012. Guidance on the assessment of additives intended to be used in pets and other non food-producing animals. *EFSA Journal* 2011;9(2):2012, 3 pp. doi:10.2903/j.efsa.2011.2012
- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012. Guidance for the preparation of dossiers for nutritional additives. *EFSA Journal* 2012;10(1):2535, 14 pp. doi:10.2903/j.efsa.2012.2535
- EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2014. Scientific Opinion on the safety and efficacy of inositol as a feed additive for fish, dogs and cats. *EFSA Journal* 2014; 12(5):3671, 19 pp. doi:10.2903/j.efsa.2014.3671
- Jiang W-D, Feng L, Liu Y, Jiang J and Zhou X-Q, 2009. Growth, digestive capacity and intestinal microflora of juvenile Jian carp (*Cyprinus carpio* var. Jian) fed graded levels of dietary inositol. *Aquaculture Research*, 40, 955–962.
- Pallauf J and Rimbach G, 1997. Nutritional significance of phytic acid and phytase. *Archives of Animal Nutrition*, 50, 301–319.
- Shiau S-Y and Su SL, 2004. Dietary inositol requirement for juvenile grass shrimp, *Penaeus monodon*. *Aquaculture*, 241, 1–8.
- Shiau S-Y and Su S-L, 2005. Juvenile tilapia (*Oreochromis niloticus* × *Oreochromis aureus*) requires dietary myo-inositol for maximal growth. *Aquaculture*, 243, 273–277.
- Waagbø R, Sandnes K and Lie Ø, 1998. Effect of inositol supplementation on growth, chemical composition and blood chemistry in Atlantic salmon, *Salmo salar* L., fry. *Aquaculture Nutrition*, 4, 53–59.
- Watson AL, Fray TR, Bailey J, Baker CB, Beyer SA and Markwell PJ, 2006. Dietary constituents are able to play a beneficial role in canine epidermal barrier function. *Experimental Dermatology*, 15, 74–81.

Abbreviations

ADME	absorption, distribution, metabolism and excretion
EC	European Commission
FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
GC	gas chromatography
LOQ	limit of quantification
ME	metabolisable energy