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Safety and efficacy of maltol belonging to chemical group 12 when used as flavouring for all animal species

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Abstract

Following a request from the European Commission, the EFSA 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 maltol, a compound belonging to chemical group 12 (maltol derivatives and ketodioxane derivatives). Maltol is currently authorised as a flavour in food. The FEEDAP Panel concludes that maltol added to the feed of all animal species is safe at the normal use level of 5 mg/kg feed. The high use level of 25 mg/kg feed is safe for all animal species except for piglets, chickens for fattening, laying hens and cats. No safety concern would arise for the consumer from the use of these compounds up to the highest proposed level in feeds. No specific data on the safety for the user were provided. In the material safety data sheet, hazards for skin and eye contact and respiratory system are recognised for maltol. The proposed maximum use level in feed for maltol is unlikely to pose a risk for the terrestrial and fresh water environments. Because maltol is used in food as flavouring, and its function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

Keywords: Sensory additives, flavourings, maltol derivatives and ketodioxane derivatives, chemical group 12, maltol

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003[1] 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; in addition, Article 10(2) of that Regulation also specifies that for existing products within the meaning of Article 10(1), an application shall be submitted in accordance with Article 7, within a maximum of 7 years after the entry into force of this Regulation.

The European Commission received a request from Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG)[2] for authorisation of maltol, when used as a feed additive for all animal species (category: sensory additives; functional group: flavourings). Chemical group (CG) 12 for flavouring substances is defined in Commission Regulation (EC) No 1565/2000[3] as 'maltol derivatives and ketodioxane derivatives'.

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 and under Article 10(2) (re-evaluation of an authorised feed additive). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 10 September 2010.

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 on the efficacy of maltol, when used under the proposed conditions of use (see Section 3.1.2).

1.2. Additional information

Maltol has been assessed by the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and was considered safe for use in food (WHO 1981a,b, 2006). In 1981, JECFA established an acceptable daily intake (ADI) value of 1 mg/kg body weight (bw) per day, which was maintained in 2006. Subsequently, the EFSA Panel on Food Additive, Flavourings, Processing Aids and Materials in Contact with Food (AFC) considered maltol for use as food flavouring and raised a concern for genotoxicity (EFSA, 2009). In order to clarify the genotoxic potential of maltol, the EFSA Panel on Food Contact Materials and Processing (CEF) requested additional data including a micronucleus assay after oral application and an *in vivo* Comet assay (EFSA CEF Panel, 2014). Having received and considered this additional data, the CEF Panel in its final assessment concluded that there was no concern for genotoxicity (EFSA CEF Panel, 2015).

Maltol is currently listed in the European Union database of flavouring substances[4] and in the European Union Register of Feed Additives, and thus authorised for use in food and feed in the European Union (EU). It has not been previously assessed by EFSA as feed additive.

Regulation (EC) No 429/2008[5] allows substances already approved for use in human food to be assessed with a more limited procedure than for other feed additives. However, the use of this procedure is always subject to the condition that food safety assessment is relevant to the use in feed.

[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] On 13/3/2013, EFSA was informed by the applicant that FFAC EEIG was liquidated on 19/12/2012 and their rights as applicant were transferred to FEFANA Asbl (EU Association of Specialty Feed Ingredients and their Mixtures), Avenue Louise 130A, Box 1, 1050 Brussels, Belgium.

[3] Commission Regulation (EC) No 1565/2000 of 18 July 2000 laying down the measures necessary for the adoption of an evaluation programme in application of Regulation (EC) No 2232/96 of the European Parliament and of the Council. OJ L 180, 19.7.2000, p. 8.

[4] Commission Implementing Regulation (EU) No 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. OJ L 267, 2.10.2012, p. 1.

[5] 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.

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier[6] in support of the authorisation request for the use of maltol as a feed additive. The technical dossier was prepared following the provisions of Article 7 of Regulation (EC) No 1831/2003, Regulation (EC) No 429/2008 and the applicable EFSA guidance documents.

The EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) has sought to use the data provided by the applicant together with data from other sources, such as previous risk assessments by EFSA or other expert bodies, peer-reviewed scientific papers and experts' knowledge, to deliver the present output.

EFSA has verified the European Union Reference Laboratory (EURL) report as it relates to the methods used for the control of maltol in animal feed. The Executive Summary of the EURL report can be found in Annex A.[7]

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of maltol is in line with the principles laid down in Regulation (EC) No 429/2008[5] and the Guidance for the preparation of dossiers for sensory additives (EFSA FEEDAP Panel, 2012a), Technical Guidance for assessing the safety of feed additives for the environment (EFSA, 2008), Guidance for the preparation of dossiers for additives already authorised for use in food (EFSA FEEDAP Panel, 2012b), Guidance for establishing the safety of additives for the consumer (EFSA FEEDAP Panel, 2012c), and Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012d).

3. Assessment

3.1. Characterisation

The molecular structure of maltol is shown in Figure 1 and, its physicochemical characteristics are summarised in Table 1.

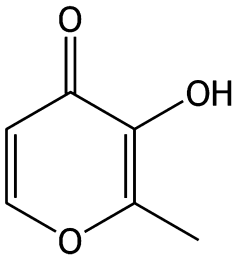

Figure 1: Molecular structure of maltol

Table 1: Chemical Abstracts Service (CAS) and FLAVIS numbers and some characteristics of maltol

EU register name	CAS no.	Flavis no.	Molecular formula	Molecular weight	Physical status	Log K_{ow} [(a)]
Maltol	118-71-8	07.014	$C_6H_6O_3$	126.11	Solid	0.09

FLAVIS: The EU Flavour Information System.
(a): Logarithm of octanol–water partition coefficient.

Maltol is largely produced by chemical synthesis (e.g. by the alkaline hydrolysis of streptomycin salts; also from piperidine to pyromeconic acid and subsequent methylation at the 2 position).[8]

[6] FEED dossier reference: FAD-2010-0064.
[7] The full report is available on the EURL website: http://irmm.jrc.ec.europa.eu/SiteCollectionDocuments/FinRep-FAD-2010-0064.pdf
[8] Technical dossiers/Section II.

Data were provided for the batch-to-batch variation in eight batches which gave an average of 99.7% (range 99.5–99.9%).[9] The content of the active substance exceeded the JECFA specifications of 99% (Combined Compendium of Food Additives Specifications; FAO, 2006).

Potential contaminants are considered as part of the product specification and are monitored as part of the Hazard Analysis and Critical Control Point procedure applied by all consortium members. The parameters considered include residual solvents, heavy metals and other undesirable substances. However, no evidence of compliance was provided for these parameters.

3.1.1. Stability

A shelf life of at least 24 months is given for maltol when stored in closed containers under recommended conditions.[8] This assessment is made on the basis of compliance with the original specification over this storage period.

3.1.2. Conditions of use

The applicant proposes the use of maltol in feed for all animal species without withdrawal time at a normal use level of 5 mg/kg feed and a high use level of 25 mg/kg feed.

3.2. Safety

The assessment of safety is based on the high use level proposed by the applicant (25 mg/kg complete feed).

3.2.1. Absorption, distribution, metabolism and excretion (ADME)

It was demonstrated that maltol rapidly crosses the brush border membrane of rat duodenal segments *in vitro* and enters the intestinal cells in a concentration-dependent manner (Barrand et al., 1987; Levey et al., 1988). Extensive and rapid absorption is also found in the dog (Rennhard, 1971). *In vivo* studies with a maltol/iron complex have shown that after intraduodenal administration maltol metabolites can be detected in the blood within 2 min (Barrand et al., 1987).

Following absorption, maltol is metabolised by glucuronidation and/or sulfation in the intestinal cells and the liver. *In vitro* experiments with rat liver homogenates demonstrated a rapid and complete conjugation of maltol (Barrand et al., 1987; Barrand and Callingham, 1991; Barrand et al., 1991).

Conjugation of maltol with glucuronic acid and sulfate were also observed after intravenous (i.v.) administration to dogs (Rennhard, 1971).

Maltol is excreted rapidly in the urine, mainly in the form of conjugated metabolites (Barrand and Callingham, 1991; Barrand et al., 1991) following i.v. or oral administration in the rat. After i.v. injection of 10 mg/kg maltol in dogs, 57% of the administered dose was excreted in the urine within 24 h, of which 88% was excreted within the first 6 h (Rennhard, 1971).

These findings limited to dogs and rats demonstrate that maltol is rapidly absorbed, conjugated and excreted mainly via the kidneys. No phase I metabolites have been detected. From the pharmacokinetic behaviour of maltol, tissue accumulation is not expected.

Metabolism studies of maltol in animals, other than rats and dogs, are lacking in the scientific literature. Food-producing animals, including ruminants, pigs, fish and birds are able to carry out conjugation reactions with sulfate and glucuronic acid (Watkins and Klaassen, 1986; James, 1987; Gusson et al., 2006), producing water-soluble derivatives that are eliminated in the urine. Therefore, mammals, fish and birds can also be assumed to have the ability to metabolise and excrete maltol and there is no evidence that maltol or metabolites thereof would accumulate in tissues and cause a concern for consumer safety. The FEEDAP Panel notes that for feline species the capacity for conjugation is limited (Shrestha et al., 2011; Court, 2013).

3.2.2. Toxicological studies

No studies were submitted by the applicant apart from those considered by JECFA which were made available only in summary form (King et al., 1978 as cited in WHO, 1981a). Although the FEEDAP Panel is not in a position to independently confirm the conclusions of JECFA, it accepts the

[9] Technical dossiers/Section II/Annex 2.1 and Supplementary Information June 2011.

internationally recognised ADI of 1 mg/kg bw per day derived from a no observed effect level (NOEL) of 100 mg/kg bw per day (WHO, 1981a, 2006).

3.2.3. Safety for the target species

The first approach to the safety assessment for target species takes account of the applied use levels in animal feed relative to the maximum reported exposure of humans on the basis of the metabolic body weight. Human exposure in the EU (WHO, 2006) is 3,600 μg/person and day. This corresponds to 166 μg/kg $bw^{0.75}$ per day. This exposure level is considered safe for humans by JECFA. Table 2 summarises the result of the comparison with human exposure for representative target animals. The body weight of target animals is taken from the default values shown in Table 3.

Table 2: Comparison of exposure of humans and target animals to the flavouring under application

Flavouring	Use level in feed (mg/kg)	Human exposure (μg/kg $bw^{0.75}$ per day)*	Target animal exposure (μg/kg $bw^{0.75}$ per day)		
			Salmon	Piglet	Dairy cow
Maltol	25	166	588	2,632	3,885

*: Metabolic body weight (kg $bw^{0.75}$) for a 60-kg person = 21.6.

Table 2 shows that for maltol, the proposed highest animal exposure is higher than human exposure. As an alternative, the maximum feed concentration which can be considered safe for the target animals can be derived from the NOEL of 100 mg/kg bw per day identified by JECFA in a 2-year dietary study in rats (WHO, 1981a,b, 2006). Applying an uncertainty factor (UF) of 100 to the NOEL, the maximum safe intake for the target species was derived following the EFSA Guidance for sensory additives (EFSA FEEDAP Panel, 2012a), and thus, the maximum safe feed concentration was calculated (Table 3). The UF for cats is increased by an additional factor of 5 because of the reduced capacity for glucuronidation (Court and Greenblatt, 1997).

Table 3: Maximum safe concentration in feed for different target animals for maltol [07.014]

Target animal	Default values		Maximum safe intake/feed concentration	
	Body weight (kg)	Feed intake (g/day)[(a)]	Intake (mg/day)	Concentration (mg/kg feed)[(b)]
Salmonids	2	40	2	50
Veal calves (milk replacer)	100	2,000	100	50
Cattle for fattening	400	8,000	400	44
Dairy cows	650	20,000	650	29
Piglets	20	1,000	20	20
Pigs for fattening	100	3,000	100	33
Sows	200	6,000	200	33
Chickens for fattening	2	120	2	17
Laying hens	2	120	2	17
Turkeys for fattening	12	400	12	30
Dogs	15	250	15	53
Cats[(c)]	3	60	0.6	8.8

(a): Complete feed with 88% dry matter (DM), except milk replacer for veal calves (94.5% DM), and for cattle for fattening, dairy cows, dogs and cats for which the values are DM intake.
(b): Complete feed containing 88% DM, milk replacer (94.5% DM).
(c): The uncertainty factor for cats is increased by an additional factor of 5 because of the reduced capacity of glucuronidation.

The FEEDAP panel concludes that maltol added to the feed of all animal species is safe at the normal use level of 5 mg/kg feed. The high use level of 25 mg/kg feed is safe for all animal species except for piglets, chickens for fattening, laying hens and cats.

3.2.4. Safety for the consumer

The safety for the consumer of maltol used as a food flavour has been already assessed by JECFA (WHO, 1981a,b, 2006) and EFSA (EFSA, 2009; EFSA CEF Panel 2015). This compound is currently authorised in the EU as food flavouring. Considering that JECFA (WHO, 1981a,b, 2006) set an ADI of 1 mg kg/bw per day for this compound, that at least 60% of maltol administered is excreted without being metabolised and that human exposure is around 3 mg/day (5% of the ADI), the FEEDAP Panel considers that the contribution of maltol when used as feed flavouring at the doses considered safe for the target species would not significantly contribute to the ADI.

Consequently, no safety concern would arise for the consumer from the use of maltol up to the highest safe level in feeds.

3.2.5. Safety for the user

No specific data on the safety for the user were provided. In the material safety data sheet,[10] hazards for skin and eye contact and respiratory system are recognised for maltol.

3.2.6. Safety for the environment

The additions of naturally occurring substances that will not result in a substantial increase in the concentration in the environment are exempt from further assessment. Examination of the provided literature failed to demonstrate that maltol occurs naturally at concentrations above the proposed maximum application rate of 25 mg/kg feed (data taken from the Netherlands Organisation for Applied Scientific Research (TNO) database Volatile Compounds in Food *ver.* 14.1; Burdock, 2009). Consequently, an environmental risk assessment is required.

The predicted environmental concentration for soil (PEC_{soil}) and porewater ($PEC_{porewater}$) were calculated based on the use rate of 25 mg/kg feed and compared with the trigger values for compartments set in the phase I of the relevant EFSA guidance (EFSA, 2008).

The PEC_{soil} value of 535 μg/kg soil is above the threshold of 10 μg/kg (EFSA, 2008). The PEC for pore water is dependent on the sorption. For this calculation, the substance-dependent properties (organic carbon sorption constant (K_{oc}), molecular weight, vapour pressure and solubility) are needed. These were estimated from the Simplified Molecular Input Line Entry Specification (SMILES) notation of the chemical structure using EPIWEB 4.1 (Table 4).[11] This program was also used to derive the SMILES notation from the CAS numbers. The K_{oc} value derived from the first-order molecular connectivity index was used, as recommended by the EPIWEB program.

Table 4: Physicochemical properties predicted by EPIWEB 4.1 and predicted toxicity of maltol [07.014] by ECOSAR 1.11 (based on predictions for the class vinyl/allyl/ketones)

Predicted by EPIWEB 4.1					Predicted by ECOSAR 1.11			
DT_{50}[(a)]	Molecular weight	Vapour pressure	Solubility	K_{oc}[(b)]	LC_{50}[(c)] fish	LC_{50} daphnids	EC_{50}[(d)] algae	EC_{50} earthworm
(days)	(g/mol)	(Pa)	(mg/L)	(L/kg)	(mg/L)	(mg/L)	(mg/L)	(mg/kg)
7	126.11	0.00571	79,800	1	6,058	7,979	3,041	1,719.6

(a): DT_{50}: half-life of the additive in manure.
(b): K_{oc}: organic carbon sorption constant.
(c): LC_{50}: the concentration of a test substance which results in a 50% mortality of the test species.
(d): EC_{50}: the concentration of a test substance which results in 50% of the test animals being adversely affected (i.e. both mortality and sublethal effects).

The half-life (DT_{50}) was calculated using BioWin4.1 (Ultimate Survey Model), which gives a rating number. This rating number *r* was translated into a half-life using the formula by Arnot et al. (2005):

$$DT_{50} = 10^{(-r\times 1.07+4.12)}.$$

This is the general regression used to derive estimates of aerobic environmental biodegradation half-lives from BioWin 4.1 model output.

[10] Technical dossier/Section II/Annex II.3.
[11] Available online: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm

The calculated predicted exposure for pore water ($PEC_{porewater}$) of 3,942 μg/L is above 0.1 μg/L and the predicted exposure concentration for soil (PEC_{soil}) is above 10 μg/kg. Therefore, maltol as a feed additive is the subject of phase II risk assessment.

In the absence of experimental data, the phase II risk assessment was performed using ECOSAR v1.11, which estimates the half-maximal effective concentration (EC_{50}) or lethal concentration (LC_{50}) for earthworms, fish, green algae and daphnids from the SMILES notation of the substance (Table 4). The corresponding predicted no effect concentration for aquatic compartment ($PNEC_{aquatic}$) was derived from the lowest toxicity value for freshwater environment by applying a UF of 1,000.

The estimated EC_{50} for earthworms was 1,720 mg/kg. Applying the UF of 1,000 would lead to safe concentration of maltol for soil fauna ($PNEC_{soil}$) of 1,720 μg/kg. The PEC/PNEC ratio for soil of 0.31 indicates that use of maltol at 25 mg/kg of complete feed for all species is acceptable.

The lowest estimated EC_{50} value is 3,041 mg/L for algae (Table 4). This would yield a PNEC of 3,041 μg/L using a safety factor of 1,000 according to the guidance (EFSA, 2008), which is higher than the estimated surface water concentration (1,314 μg/L), giving a PEC_{sw}/PNEC ratio of 0.44. This indicates that the application of maltol at 25 mg/kg feed for all species does not pose a risk for the environment.

The use of maltol in fish feed in land-based aquaculture systems does not give a predicted environmental concentration of the additive (parent compound) in surface water (PEC_{swaq}) above the trigger value of 0.1 μg/L when calculated according to the guidance. For sea cages, a dietary concentration of 0.047 mg/kg would ensure that the threshold for the predicted environmental concentration of the additive (parent compound) in sediment (PEC_{sed}) of 10 μg/kg is not exceeded, when calculated according to the EFSA guidance (EFSA, 2008).

In the absence of data and solely based on modelled predictions of environmental fate and toxicity, the use of maltol as a feed additive for all animal species at 25 mg/kg feed is not expected to pose a risk for the terrestrial and fresh water environments. For the marine environment, the safe use level is estimated to be 0.05 mg/kg feed.

3.3. Efficacy

Since this compound is used in food as flavouring, and its function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

4. Conclusions

The FEEDAP Panel concludes that maltol added to the feed of all animal species is safe at the normal use level of 5 mg/kg feed. The high use level of 25 mg/kg feed is safe for all animals species except for piglets, chickens for fattening, laying hens and cats.

No safety concern would arise for the consumer from the use of maltol up to the highest proposed level in feeds.

No specific data on the safety for the user were provided. In the material safety data sheet, hazards for skin and eye contact and respiratory system are recognised for maltol.

The proposed maximum use level in feed for maltol is unlikely to pose a risk for the terrestrial and fresh water environments.

Because maltol is used in food as a flavouring and its function in feed is essentially the same as that in food, no further demonstration of efficacy is necessary.

Documentation provided to EFSA

1) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). May 2010. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
2) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. May 2011. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
3) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. June 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
4) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. August 2012. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).

5) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. October 2014. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
6) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. October 2015. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
7) Chemically defined flavourings from Flavouring Group 12 - Maltol derivatives and ketodioxane derivatives (CDG 12). Supplementary information. July 2016. Submitted by Feed Flavourings Authorisation Consortium European Economic Interest Grouping (FFAC EEIG).
8) Evaluation report of the European Union Reference Laboratory for Feed Additives on the methods(s) of analysis for Chemically Defined Flavourings – Group 12 (CDG12 Maltol derivatives and ketodioxane derivatives).
9) Evaluation report of the European Union Reference Laboratory for Feed Additives on the Methods(s) of Analysis for maltol derivatives and ketodioxane derivatives.
10) Comments from Member States.

References

Arnot J, Gouin T and Mackay D, 2005. Practical Methods for Estimating Environmental Biodegradation Rates, Report to Environment Canada. CEMN Report No 200503. Canadian Environmental Modelling Network, Trent University, Peterborough, ON, Canada.

Barrand MA and Callingham BA, 1991. Evidence for regulatory control of iron uptake from ferric maltol across the small-intestine of the rat. British Journal of Pharmacology 102, 408–414.

Barrand MA, Callingham BA and Hider RC, 1987. Effects of the pyrones, maltol and ethyl maltol, on iron-absorption from the rat small-intestine. Journal of Pharmacy and Pharmacology, 39, 203–211.

Barrand MA, Callingham BA, Dobbin P and Hider RC, 1991. Dissociation of a ferric maltol complex and its subsequent metabolism during absorption across the small-intestine of the rat. British Journal of Pharmacology, 102, 723–729.

Burdock GA, 2009. Fenaroli's handbook of flavor ingredients. 6th Edition. CRC press. Taylor & Francis Group. Boca Raton, FL, 2159 pp.

Court MH, 2013. Feline drug metabolism and disposition: pharmacokinetic evidence for species differences and molecular mechanisms. Veterinarian Clinics of North America: Small Animal Practice, 43, 1039, doi:10.1016/j.cvsm.2013.05.002

Court MH and Greenblatt DJ, 1997. Molecular basis for deficient acetaminophen glucuronidation in cats. Biochemical Pharmacology, 53, 1041–1047.

EFSA (European Food Safety Authority), 2008. Technical Guidance of the Scientific Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) for assessing the safety of feed additives for the environment. EFSA Journal 2008;6(10):842, 28 pp. doi: 10.2903/j.efsa.2008.842

EFSA (European Food Safety Authority), 2009. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids on a request from the Commission on Flavouring Group Evaluation 213: alpha,beta-Unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19. EFSA Journal 2009;ON-879, 1–27.

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2014. Scientific Opinion on Flavouring Group Evaluation 213, Revision 1 (FGE.213Rev1): consideration of genotoxic potential for α,β-Unsaturated Alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19. EFSA Journal 2014;12(5):3661, 46 pp. 10.2903/j.efsa.2014.3661

EFSA CEF Panel (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids), 2015. Scientific Opinion on Flavouring Group Evaluation 213, Revision 2 (FGE.213Rev2): consideration of genotoxic potential for α,β-unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19. EFSA Journal 2015;13(9):4244, 49 pp. doi:10.2903/j.efsa.2015.4244

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012a. Guidance for the preparation of dossiers for sensory additives. EFSA Journal 2012;10(1):2534, 26 pp. doi:10.2903/j.efsa.2012.2534

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012b. Guidance for the preparation of dossiers for additives already authorised for use in food. EFSA Journal 2012;10(1):2538, 4 pp. doi:10.2903/j.efsa.2012.2538

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012c. Guidance for establishing the safety of additives for the consumer. EFSA Journal 2012;10(1):2537, 12 pp. doi:10.2903/j.efsa.2012.2537

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2012d. Guidance on studies concerning the safety of use of the additive for users/workers. EFSA Journal 2012;10(1):2539, 5 pp. doi:10.2903/j.efsa.2012.2539

FAO (Food and Agricultural Organization of the United Nations), 2006. FAO JECFA Monographs 1: Combined Compendium of Food Additive Specifications—Joint FAO/WHO Expert Committee on Food Additives—All specifications monographs from the 1st to the 65th meeting (1956–2005). Volume 4. Analytical methods, test procedures and laboratory solutions used by and referenced in the food additive specifications. Food and Agricultural Organization of the United Nations, Rome Italy. Available online: http://www.fao.org/docrep/009/a0691e/a0691e00.htm

Gusson F, Carletti M, Giuliano Albo A, Dacasto M and Nebbia C, 2006. Comparison of hydrolitic and conjugative biotransformations pathways in horse, cattle, pig, broiler chick, rabbit and rat liver subcellular fractions. Veterinary Research Communications 30, 271–283.

James MO, 1987. Conjugation of organic pollutants in aquatic species. Environmental Health Perspectives, 71, 97–103.

Levey JA, Barrand MA, Callingham BA and Hider RC, 1988. Characteristics of iron(iii) uptake by isolated fragments of rat small-intestine in the presence of the hydroxypyrones, maltol and ethyl maltol. Biochemical Pharmacology, 37, 2051–2057.

Rennhard HH, 1971. The metabolism of ethyl maltol and maltol in the dog. Journal of Agricultural and Food Chemistry, 19, 152–154.

Shrestha B, Reed JM, Starks PT, Kaufman GE, Goldstone JV, Roelke ME, O'Brien SJ, Koepfli K-P, Framk LG and Court MH, 2011. Evolution of a major drug metabolizing enzyme defect in the domestic cat and other felidae: phylogenetic timing and the role of hypercarnivory. PLoS ONE 6: e18046. doi: 10.1371/journal.pone.0018046

Watkins JB III and Klaassen CD, 1986. Xenobiotic biotransformation in livestock: comparison to other species commonly used in toxicity testing. Journal of Animal Science, 63, 933–942.

WHO (World Health Organisation), 1981a. Toxicological evaluation of certain food additives. WHO Food Additives Series, No. 16. Available online: http://www.inchem.org/documents/jecfa/jecmono/v16je15.htm

WHO (World Health Organisation), 1981b. Evaluation of certain food additives (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.

WHO (World Health Organisation), 2006. Evaluation of certain food additives (Sixty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 934, 2006.

Abbreviations

ADI	average daily intake
ADME	absorption, distribution, metabolism and excretion
AFC	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
bw	body weight
CAS	Chemical Abstracts Service
CD	Commission Decision
CDG	chemically defined group
CEF	EFSA Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CG	chemical group
DM	dry matter
DT_{50}	degradation half-time
EC_{50}	half-maximal effective concentration
ECOSAR	component program of EPI suite™
EEIG	European Economic Interest Grouping
EPI suite	Estimation Programs Interface (EPI) Suite™
EURL	European Union Reference Laboratory
FAO	Food Agricultural Organization
FEEDAP	EFSA Scientific Panel on Additives and Products or Substances used in Animal Feed
FFAC	Feed Flavourings authorisation Consortium of FEFANA (EU Association of Specialty Feed Ingredients and their Mixtures)
FGE	food group evaluation
FLAVIS	The EU Flavour Information System
FL-no	FLAVIS number
GC–MS	gas chromatography–mass spectrometry
i.v.	intravenous
JECFA	The Joint FAO/WHO Expert Committee on Food Additives

K_{oc}	organic carbon sorption constant
K_{ow}	octanol–water partition coefficient
LC_{50}	lethal concentration, median
Log K_{ow}	logarithm of octanol-water partition coefficient
MW	molecular weight
NOEL	no observed effect level
PEC	predicted environmental concentration
$PEC_{porewater}$	predicted environmental concentration for porewater
PEC_{soil}	predicted environmental concentration for soil
PEC_{sed}	predicted environmental concentration of the additive (parent compound) in sediment
PEC_{swaq}	predicted environmental concentration of the additive (parent compound) in surface water
PNEC	predicted no effect concentration
$PNEC_{aquatic}$	predicted no effect concentration for aquatic compartment
$PNEC_{soil}$	predicted no effect concentration for soil
$PNEC_{sw}$	predicted no effect concentration for surface water
RTL	retention time locking
TNO	Netherlands Organisation for Applied Scientific Research
UF	uncertainty factor
WHO	World Health Organization

Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of Analysis for Chemically Defined Flavourings – Group 12 (CDG12 Maltol derivatives and ketodioxane derivatives)

Authorisation as feed additives is sought under the category 'sensory additives', functional group 2 (b) 'flavouring compounds', according to the classification system of Annex I of Regulation (EC) No 1831/2003 for the following two applications:

- *Chemically Defined Flavourings – Group 12 (Maltol derivatives and ketodioxane derivatives, FAD-2010-0064) and*
- *Chemically Defined Flavourings – Group 17 (Propenylhydroxybenzenes – Isoeugenol, FAD–2010-0065).*

In the current applications submitted according to Article 4(1) and Article 10 (2) of Regulation (EC) No 1831/2003, the authorisation for all species and categories is requested. *Maltol* and *Isoeugenol* have a minimum purity of 98% and 99%, respectively.

Maltol and *Isoeugenol* are intended to be incorporated only into *feedingstuffs* or drinking *water*. The Applicant suggested no minimum or maximum levels for the different flavouring compounds in *feedingstuffs*.

For the identification of volatile chemically defined flavouring *Maltol* and *Isoeugenol* in the *feed additive,* the Applicant submitted a qualitative multianalyte gas chromatography–mass spectrometry (GC–MS) method, using retention time locking (RTL), which allows a close match of retention times on GC–MS. By making an adjustment to the inlet pressure, the retention times can be closely matched to those of a reference chromatogram. It is then possible to screen samples for the presence of target compounds using a mass spectral database of RTL spectra. The Applicant maintained two FLAVOR2 databases/libraries (for retention times and for MS spectra) containing data for more than 409 flavouring compounds. These libraries were provided to the CRL. The Applicant provided the typical chromatogram for *Maltol* and *Isoeugenol*.

In order to demonstrate the transferability of the proposed analytical method (relevant for the method verification), the Applicant prepared a model mixture of flavouring compounds on a solid carrier to be identified by two independent expert laboratories. This mixture contained 20 chemically defined flavourings belonging to 20 different chemical groups to represent the whole spectrum of compounds in use as feed flavourings with respect to their volatility and polarity. Both laboratories properly identified all the flavouring compounds in all the formulations. Since *Maltol* and *Isoeugenol* are within the volatility and polarity range of the model mixture tested, the Applicant concluded that the proposed analytical method is suitable to determine qualitatively the presence of *Maltol* and *Isoeugenol* in the *feed additive.*

Based on the satisfactory experimental evidence provided, the CRL recommends for official control for the qualitative identification of *Maltol derivatives and ketodioxane derivatives,* [FAD-2010-0064] or *Propenylhydroxybenzenes – Isoeugenol,* [FAD–2010-0065]) in the *feed additive* the GC–MS–RTL (Agilent specific) method submitted by the Applicant.

As no experimental data were provided by the Applicant for the identification of the *active substances* in *feedingstuffs* and *water*, no methods could be evaluated. Therefore, the CRL is unable to recommend a method for the official control to identify *Maltol derivatives and ketodioxane derivatives,* [FAD-2010-0064] and *Propenylhydroxybenzenes – Isoeugenol,* [FAD–2010-0065]) in *feedingstuffs* or *water*.

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.