Safety and efficacy of a feed additive consisting of glyceryl polyethyleneglycol ricinoleate (PEG castor oil) for all animal species (FEFANA asbl)

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Abstract

Following a request from the European Commission, EFSA was asked to deliver a scientific opinion on the safety and efficacy of glyceryl polyethyleneglycol ricinoleate (PEG castor oil) as technological feed additive for all animal species. PEG castor oil is safe at a maximum concentration in complete feed of 90 mg/kg for chickens for fattening and other minor growing poultry; 134 mg/kg for laying hens and other laying/breeding birds kept for egg production/reproduction; 121 mg/kg for turkeys for fattening; 162 mg/kg for piglets and other minor growing Suidae; 194 mg/kg for pigs for fattening; 236 mg/kg for sows other minor reproductive Suidae; 231 mg/kg for dairy cows and other dairy ruminants (other than sheep/goats); 142 mg/kg in rabbits and 377 mg/kg in veal calves; 356 mg/kg for cattle for fattening and other growing ruminants, sheep, goat, horses and cats; 427 mg/kg for dogs; 407 mg/kg for salmonids and other fin fish; and 1,584 mg/kg for ornamental fish. For other growing species and non-food producing animals, the additive is considered safe at 90 mg/kg complete feed. The use of PEG castor oil as feed additive for all animal species would be of no concern for the consumer. The FEEDAP Panel considered inhalation exposure of the user to the additive unlikely. PEG castor oil is not considered a skin sensitiser. The panel was not in the position to conclude on the potential of the additive to be a skin or eye irritant. The additive is a readily biodegradable substance and is not expected to pose a risk for the environment. The lack of sufficient data does not allow the FEEDAP Panel to conclude on the efficacy of PEG castor oil as an emulsifier in feedingstuffs.

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Keywords: glyceryl polyethyleneglycol ricinoleate, PEG castor oil, technological additives, emulsifiers, all animal species, safety, efficacy

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1. Introduction

1.1. Background and Terms of Reference

Regulation (EC) No 1831/2003\textsuperscript{1} establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, 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, at the latest 1 year before the expiry date of the authorisation given pursuant to Directive 70/524/EEC for additives with a limited authorisation period, and within a maximum of 7 years after the entry into force of this Regulation for additives authorised without a time limit or pursuant to Directive 82/471/EEC.

The European Commission received a request from FEFANA asbl\textsuperscript{2} for the re-evaluation of the additive consisting of polyethyleneglycol ricinoleate (PEG castor oil), when used as a feed additive for all animal species (category: technological additives; functional group: emulsifiers).

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 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 30 May 2013.

According to Article 8 of Regulation (EC) No 1831/2003, 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. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the feed additive consisting of polyethyleneglycol ricinoleate (PEG castor oil), when used under the proposed conditions of use (see Section 3.1.3).

1.2. Additional information

The additive is a preparation containing polyethyleneglycol ricinoleate. It is included in the European Union Register of Feed Additives pursuant to Regulation (EC) No 1831/2003. It has not been previously assessed as a feed additive in the European Union.

The EFSA ANS Panel delivered an opinion in 2017 (EFSA ANS Panel, 2017) on the safety of a food additive based on castor oil (polyglycerol polyricinoleate).

The European Agency for the Evaluation of Medicinal Products (EMA) evaluated in 1999 (EMA, 1999) polyoxyl castor oil and polyoxyl hydrogenated castor oil.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the safety of castor oil in 1979 (JECFA, 1979).

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\textsuperscript{3} in support of the authorisation request for the use of glyceryl polyethyleneglycol ricinoleate (PEG castor oil) as a feed additive.

The FEEDAP Panel used 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 other scientific reports, 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 the polyethyleneglycol ricinoleate in animal feed. The Executive Summary of the EURL report can be found in Annex A.\textsuperscript{4}

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\textsuperscript{1} Regulation (EC) No 1831/2003 of the European Parliament and of the council of 22 September 2003 on the additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

\textsuperscript{2} FEFANA asbl, Avenue Louise 130 A, Box 1, 1,050 Brussels, Belgium.

\textsuperscript{3} FEED dossier reference: FAD-2010-0126.

\textsuperscript{4} The full report is available on the EURL website: https://joint-research-centre.ec.europa.eu/eurl-fa-eurl-feed-additives/eurl-fa-authorisation/eurl-fa-evaluation-reports_en.
2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of an active substance (trade name of the product) is in line with the principles laid down in Regulation (EC) No 429/2008 and the relevant guidance documents: Guidance on studies concerning the safety of use of the additive for users/workers (EFSA FEEDAP Panel, 2012), Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017a), Guidance on the identity, characterisation and conditions of use of feed additives (EFSA FEEDAP Panel, 2017b), Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c), Guidance on the assessment of the efficacy of feed additives (EFSA FEEDAP Panel, 2018), Guidance on the assessment of the safety of feed additives for the environment (EFSA FEEDAP Panel, 2019).

3. Assessment

The additive under assessment, glyceryl polyethyleneglycol ricinoleate, is intended to be used as a technological additive (functional group: emulsifiers) in feed for all animal species.

3.1. Characterisation

3.1.1. Characterisation of the additive

The additive glyceryl polyethyleneglycol ricinoleate, hereafter called PEG X castor oil (X = 6.5 to 200) (synonyms: polyethylene glycol (PEG) castor oil, castor oil ethoxylate, (poly)ethoxylated castor oil, macrogolglycerol ricinoleate; Chemical Abstract Service (CAS) number 61791-12-6), is manufactured by the addition of X moles of ethylene oxide per mole of castor oil, in a chemical synthesis process characterised by two steps. In the first one, castor oil is heated at a minimum of 100°C, with an alkaline catalyst, and then subject to vacuum application, in order to minimise the water content. In a second step, ethylene oxide is added, at temperature and pressure of 120–180°C and 0.5–6 bar, respectively. Ethylene oxide and 1,4-dioxane are removed with a stream of nitrogen and/or steam at elevated temperature, and by applying vacuum, then the temperature is lowered to < 70°C. This process leads to the formation of a mixture of species (A, B, C and D), which are present in the additive in variable proportions: tri-ricinoleate esters of ethoxylated glycerol (PEG castor oil, the predominant species) (A), polyoxyethylene glycol (macrogl) ricinoleates (B), ethoxylated glycerols (C) and polyethylene glycols (D). A partial ethoxylation of the hydroxyl groups of the fatty acid chains (i.e. the ricinoleyl moieties) in the (A) species may also occur. The structural formulae of PEG castor oil species are described in Figure 1.

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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.

6 In the current applicant, data has been provided by X companies, involved in the manufacturing and/or distribution of the additive, which produce/distribute one or more of the different PEG X castor oil.
The analysis of four commercial batches of PEG 15 castor oil\(^7\) from one company showed that 80–82.6% of the additive was composed of PEG castor oil in which the hydroxyl group of the fatty acid chains of species A was not ethoxylated. A minor fraction was partially ethoxylated, with one (5.6–6.1%), two (2.3–2.5%) or three (1.0–1.1%) ethylene oxide units on the hydroxyl group of the fatty acid chain. The combined concentrations of ethoxylated glycerols and polyethylene glycols (species C and D) were in the range 6.2–7.9%. The fatty acid profile of the same four batches showed that ricinoleic acid represents 87.9–88.4% of total fatty acids, followed by oleic acid (4.4–4.5%), stearic and palmitic acid (both in the range 1.6–1.7%) and linoleic acid (0.8–0.9%).

The identity of the additive was confirmed in the same four batches with \(^1\)H-NMR (nuclear magnetic resonance) analysis and with IR (infrared) spectroscopy in one batch each of PEG 15-, PEG 19- and PEG 200 castor oil from a second company, and of PEG 20- and PEG 36 castor oil from a third company.\(^7\)

The additive is specified to have a saponification value of 16–162 mg KOH/g, pH in the range 5.5–7.5, acid value in the range 0–2 mg KOH/g and water content in the range 0–3%. The additive is also specified to contain ethylene oxide ≤ 1 mg/kg and 1,4-dioxane ≤ 5 mg/kg, as residual impurities from the synthetic process. Five batches each of different PEG X castor oils (X: 15; 18; 19; 20; 34; 36; 30–40; 200) produced from six companies were analysed,\(^7\) showing compliance with the specifications. The concentrations of lead, cadmium, mercury and arsenic in the same batches were below the proposed specifications (≤ 5, ≤ 1, ≤ 1 and ≤ 3 mg/kg for lead, cadmium, mercury and arsenic, respectively). None of them raises a safety concern. Six commercial batches of PEG castor oil were analysed for pesticides, which were all below the respective limits of detection.\(^7\) No data on the presence of dioxins and polychlorinated biphenyls (PCBs) were submitted.

According to the applicant, the manufacturing conditions (temperature > 100°C and pressure up to 6 bar), the use of the ethylene oxide in the process and the low water content (< 3%) would minimise the potential for microbial growth in the additive. The analysis of five batches each of a PEG 18 castor oil and of a PEG 34 castor oil,\(^7\) from two companies, showed that the total plate count was always < 10 CFU/g additive.

PEG castor oil may vary in appearance from yellow liquid (low degree of ethoxylation) to wax-like semisolid (high degree of ethoxylation). PEG castor oil is soluble in water, with the extent of solubility increasing with the number of polyoxyethylene units (hydrophilic moiety). It is also soluble in dichloromethane and alcohol but has a low solubility in lipids.

### 3.1.2. Stability and homogeneity

The shelf-life of the additive was studied by analysing the saponification value (mg KOH/g), the pH of a 1% solution, the acid value (mg KOH/g), the water content (%), the concentrations of ethylene oxide and 1,4-dioxane and the cloud point (°C) of one batch of a PEG 18 castor oil stored for 18 and 36 months and one batch each of PEG 15 castor oil and PEG 19 castor oil stored for 36 months, and

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7 Technical dossier/Section II/Annex II_1_Analytical_data.
one of PEG 200 castor oil stored for 15 months. The results, reported in tabular form and not supported by certificates of analysis, showed that essentially no changes occurred on the parameters measured over the storage period.

For technological additives, stability could be demonstrated by the persistence of the effect, and no demonstration of homogenous distribution is considered necessary once the efficacy of the additive as emulsifier is demonstrated (see Section 3.2.7).

3.1.3. Conditions of use

PEG castor oil is intended to be used as an emulsifier in feedingstuffs for all animal species, without indication for a minimum or maximum content. The applicant reported typical use levels in premixtures and feedingstuffs. In particular, the additive is used in fish feed up to 10,000 mg/kg and in milk replacers up to 20,000 mg/kg.

3.2. Safety

To support the safety of the additive, the applicant provided specific studies done with the additive under assessment, which are described below in the relevant sections. In addition, the applicant performed a literature search, done using a number of databases, covering the period until 2009, and using as keywords: PEG ethoxylated castor oils, including synonyms and CAS number and a number of safety-related terms. The vast majority of the studies retrieved referred to PEG castor oil used as vehicle for drugs in toxicological studies. The studies considered relevant for the assessment of the safety of the additive were submitted and used by the FEEDAP Panel to evaluate the safety of the additive.

3.2.1. Absorption, distribution, metabolism and excretion

No specific studies done with the additive under assessment were submitted.

Data on absorption, distribution, metabolism and excretion (ADME) of compounds of similar chemical structure have been assessed by EFSA (i.e. polyethylene glycol fatty acid esters, EFSA ANS Panel, 2017 and polyethylene sorbitan mono-laurate, EFSA FEEDAP Panel, 2016) or published, i.e. polyethylene glycerol polyricinoleate (Howes et al., 1998). The FEEDAP Panel noted that, like PEG castor oil, these compounds harbour an ether linkage of polyethylene glycol to an alcohol moiety (sorbitol and glycerol, respectively) and an ester linkage of free hydroxyl functions with fatty acids. The main elements of the metabolic fate of these compounds can be summarised as follows: (i) the ester link between fatty acids and hydroxyl groups is hydrolysed by pancreatic lipases followed by the metabolism of the fatty acid moiety, (ii) due to the stability of the ether linkage between polyethylene glycol and alcohols, these highly hydrophilic complexes remain essentially unchanged; they are mainly excreted in the faeces but also in the urine and their deposition in tissues and organs is negligible. The FEEDAP Panel assumed that a similar metabolic fate would occur for PEG castor oil after oral administration. Where the specific ester with ricinoleic acid is concerned, the 12-hydroxy group of the acid is involved in a similar metabolically stable ether link with polyethylene glycol. Castor oil and ricinoleic acid behave the same as other hydroxy-fatty acids, undergoing β-oxidation and limited epoxidation (JECFA, 1979; EFSA ANS Panel, 2017).

The pancreas is generally assumed to be the major source of digestive lipase enzymes in fish as it is in mammals (Tocher, 2003). The same has been shown to occur in birds (Krogdahl, 1985). Consequently, the resulting alcohol/polyethylene glycol ether is assumed to be released in the digestive tract and poorly absorbed also in these species and that no accumulation would occur in fish and bird edible tissues.

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8 technical dossier/Section III/Section III.
9 Medline, Biosis Previews, Agricola, Allied & Complementary Medicine, Mantis, Foodline: Science, CAB Abstracts, Federal Register, Elsevier Biobase, Foodline: Market, Embase, Diogenes, FDA News Mar., Adis Clinical Trials Insight and BCC Market Research.
10 (toxic? or mortal? or lethal? or adverse? or safe? or risk?) and (tumor? or tumour? Or carcino? or neoplas? or cancer?) and (terato? or teratogen? or (reproductive?) or developmental?) and (toxic? or effect? or pregnant? or fetus or fetal or litter or reproductive? or developmental?) and (foetus? or malformation? or birth?) and (fetotoxic? or development?) and (genotox? or mutagen? or Ames or dna()repair or lesion?) or micronucle? or clastogen? or chromosom? or cytogen? or cytotox? or genetic()activity or sister(chromatid()exchange?) or crosslink?) and (metabolism? or metabolic? or metabolic?) and (fate? or path?) or absorb? or absorb? or excret? or eliminat? or distribution or distribute?).
11 Technical dossier/Section III/Section III_Safety.
3.2.2. Toxicological studies

In the available toxicological studies, PEG castor oils manufactured with different numbers of moles of ethylene oxide per mole of castor oil were tested (PEG 15 and PEG 40 in the genotoxicity studies and PEG 40 in the repeated dose toxicity studies). Considering the ADME of PEG castor oil, the FEEDAP Panel considered that the results obtained in these studies could be used to cover the different PEG castor oils subject in the current application.

3.2.2.1. Genotoxicity studies, including mutagenicity

PEG castor oil was used as solvent control in several in vitro and in vivo genotoxicity studies retrieved in the literature (Kortselius, 1978; Machemer and Lorke, 1978; Blazak et al., 1988), in which no genotoxic effects were reported. In addition, a bacterial reverse mutation test, two in vitro mammalian cell micronucleus tests and an in vivo mammalian erythrocyte micronucleus test performed with PEG castor oil as test item were made available by the applicant.

3.2.2.1.1. Bacterial reverse mutation test

A reverse mutation assay in Salmonella Typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 was carried out with PEG 15 castor oil at concentrations up to 5,000 μg/plate in the presence and absence of metabolic activation (S9-mix) in compliance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 471. There was no induction of gene mutation in any tester strain in the presence and absence of S9-mix.

3.2.2.1.2. In vitro mammalian cell micronucleus test

Two in vitro micronucleus tests were performed.

In the first study, potential of PEG 40 castor oil to induce micronuclei was investigated in human lymphocytes cultured in vitro in the absence and presence of metabolic activation in compliance with OECD TG 487.

A short treatment (4 h + 18 h of recovery) in the absence and presence of metabolic activation and a continuous treatment (23 h + 0 h recovery) in the absence of metabolic activation were applied. The following concentrations were tested: 0.25, 0.5, 1.0 and 2.0 μL/mL. No statistically significant increase in the frequency of binucleated cells with micronuclei was observed after short treatment without metabolic activation. After continuous treatment, a concentration-related, statistically significant increase in the frequency of micronucleated cells was reported. These increases were observed in the presence of excessive level of cell mortality and remained within the range of historical solvent control values. A statistically significant increase of micronuclei was also induced by short treatment in the presence of metabolic activation at the top concentration of 2.0 μL/mL. Values of micronucleus frequency were within the historical solvent control range. On this basis, the FEEDAP Panel considered the results of this study not biologically relevant.

In the second study, the potential of PEG 40 castor oil to induce micronuclei was investigated in cultured human peripheral blood lymphocytes in vitro in compliance with OECD TG 487. Human lymphocytes in whole blood culture were exposed to the test item for 3 h (+17 h recovery) both in the absence and presence of exogenous metabolic activation (S9-mix) for 20 h (+0 h recovery) in the absence of S9-mix.

No cytotoxicity was observed after the short treatment with and without S9-mix up to a maximum concentration of 2000 μg/mL. After continuous treatment, a reduction in the cytokinesis-block proliferative index (CBPI) equivalent to 60% cytostasis compared with vehicle control values, was obtained with the test item at 400 μg/mL, selected as the maximum concentration for the analysis of micronuclei. No precipitation was reported at any concentration. PEG 40 castor oil did not cause any statistically significant increase in the frequency of micronuclei in binucleated cells when compared with the vehicle controls. The FEEDAP Panel concludes that the test item did not induce structural and numerical chromosomal damage in vitro in mammalian cells under the experimental conditions of this study.

12 Technical dossier/Section III/Annex III.2.32.
13 Technical dossier/Supplementary Information June 2017/Annex_Q1_in vitro MNT_Final report_LAUS and Supplementary Information December 2021/Annex_02_Sin_3_in_vitro_MNT_Laus_revised.
14 Technical dossier/Supplementary Information December 2021/Annex_02_Sin_3_in_vitro_MNT_Labcorp.
3.2.2.1.3. In vivo mammalian erythrocyte micronucleus test

In an in vivo micronucleus assay (Au et al., 1991), PEG 40 castor oil was administered by gavage to groups of five male adult ICR mice at 0.03, 0.3 and 3%. The animals were killed 30 h after treatment and bone marrow was harvested for examination. No increase in the frequency of micronucleated erythrocytes was induced by the test item. No toxicity was observed in the bone marrow as indicated by comparable PCE/NCE ratios between treated and control groups. The Panel noted that there is no evidence that the target tissue (bone marrow) was exposed to the test material.

3.2.2.2. Repeated dose toxicity studies

3.2.2.2.1. 28-day study

In a 28-day study, groups of 10 male and 10 female Sprague–Dawley rats were fed diets containing PEG 40 castor oil at concentrations of 0, 50,000 or 100,000 mg/kg (which would correspond to approximately 5,900 and 11,800 mg PEG castor oil/kg bw per day). The diets were all tolerated with no clinical signs of toxicity other than soft faeces being produced by rats in the highest dose group. There were no effects on feed intake, body weight gain, haematology (haemoglobin, red blood cell count, haematocrit, white blood cell count, differential leucocyte count) or blood biochemistry (alanine aminotransferase, cholesterol, total lipid). Increased relative weights of liver were found in the females of both treatment groups. Microscopic examination of organs and tissues revealed no treatment-related pathology. A no observed adverse effects level (NOAEL) could not be derived from this study.

3.2.2.2.2. 90-day studies

In a published 90-day study in mice (20 male and 20 female CD-1 mice), PEG 40 castor oil was used as a vehicle to administer the test item subject of the study (2,4-dichlorophenol) (Borzelleca et al., 1985). A comparison between untreated and vehicle-treated mice was used to give an indication of the toxicity of PEG 40 castor oil. The vehicle control group was given drinking water that contained 100,000 mg PEG 40 castor oil/L for 90 days, with mean fluid consumption of 219,000 mg/kg bw per day for females and 202,000 mg/kg bw per day for males (corresponding to approximately 22,000 and 20,000 mg PEG 40 castor oil/kg bw per day for females and males, respectively). Blood samples were taken at the end of the study for haematological examination and clinical chemistry. All animals were killed for necropsy, organ weights and microscopic examination of tissues and organs. Intake of drinking water was lower in the group given PEG 40 castor oil than in the untreated controls, probably due to an apparent decrease in palatability. Terminal body weights were similar for the two groups; in the PEG 40 castor oil-treated mice, absolute and relative liver and kidney weight were significantly increased while brain weight (not specified if absolute or relative) was decreased. The treated males had increased haematocrit and decreased neutrophil count. Serum levels of alkaline phosphatase and cholesterol were increased in males; albumin was increased in females; and creatinine and calcium were increased in both sexes. The BUN/creatinine ratio was increased in both sexes. No gross pathology or histopathology findings were attributable to the treatment with PEG 40 castor oil. Due to the limitations of the study (i.e. only one dose was tested), an NOAEL could not be derived from this study.

In a published 90-day study in rats (10 male and 10 female Sprague–Dawley rats), PEG 40 castor oil was used as a vehicle to administer the test item subject of the study (1,2,3- and 1,1,2 trichloropropane) (Villeneuve et al., 1985). A comparison between untreated and vehicle-treated rats was used to give an indication of the toxicity of PEG 40 castor oil. The vehicle control group was given drinking water that contained 5,000 mg PEG 40 castor oil/L (equivalent to 450 mg/kg bw per day). Intake of drinking water in the vehicle control group was slightly lower than in the untreated controls (no statistical analysis was performed). No effects of PEG 40 castor oil on body weight gain, haematology, blood biochemistry or histopathology were reported. A slightly lower relative brain weight was observed in PEG 40 castor oil-treated rats. Due to the limitations of the study (i.e. only one dose was tested), no NOAEL could be derived from this study.

In an unpublished 90-day study (reviewed by the Cosmetic Ingredient Review, 1997, no original data submitted), diets containing 100, 400, 1,600, 6,400, 25,000 and 50,000 mg PEG 40 castor oil/kg, corresponding to approximately 5, 20, 80, 320, 1,250 and 2,500 mg PEG 40 castor oil/kg bw per day, were fed to groups of 15 Sherman–Wistar rats (distribution of genders not specified). The top dose group was initially given a concentration of 100,000 mg PEG 40 castor oil/kg diet, but this caused feed...

15 Technical dossier/Section III/Annex III.2.22.
refusal, so the level was subsequently reduced to 50,000 mg/kg. A control group of 30 rats was used. Blood was sampled prior to the study and at unstated times throughout the study for haematological examination. After 8 weeks and at the end of the study, the lightest two males and two females from each group were selected for necropsy and microscopic examination of organs. The treatment had no effect on feed intake (excluding the initial 10% dietary level), body weight or haematology. No significant gross or microscopic lesions were found in any treated group. Based on the above results, the highest dose tested, 50,000 mg PEG 40 castor oil/kg (equivalent to 2,500 mg PEG 40 castor oil/kg bw per day), is regarded as the NOAEL for this study.

3.2.2.2.3. Six-month studies

In a 6-month study, groups of Sprague-Dawley rats were fed diets containing 0, 10,000, 25,000 or 50,000 mg of PEG 40 castor oil per kg diet, corresponding to approximately 0, 810, 2,050 and 4,050 mg/kg bw per day in males and 0, 964, 2,410 and 4,820 mg/kg bw per day in females. Group sizes were 35 rats per sex per group in the control and top-dose groups and 25 rats per sex per group in the low- and middle-dose groups. Blood samples were collected at days 28–30, 62–65, 125–128 and 174–177 for measurement of haemoglobin, red blood cell count, haematocrit, white blood cell count, differential leucocyte count, urea, alanine aminotransferase, cholesterol, total lipids, albumin and sugar. Urine was collected on days 28–31, 63–66, 126–129 and 175–178 for measurement of albumin, sugar, urobilinogen, sediment and pH. After 180 days on the test diets, 25 animals per sex per group were killed for necropsy and examined for gross pathology, organ weights and histopathology. The remaining animals of each sex in the control and top-dose groups were maintained on control diet for a recovery period of 42 days, before being killed and examined in a similar way. One male rat from the highest dose group died during the study. The treatment with PEG castor oil had no effect on food intake, body weight gain, haematology, blood biochemistry and urinalysis (for which detailed data were not available). At the end of the treatment period, absolute weights of liver, kidney and heart were similar in all groups, but relative weight of liver was increased in males at both the highest and the middle-dose level and in females at the middle dose only. Relative weights of heart and kidneys were increased in high-dose males. After the recovery period, there was no effect on absolute or relative weights of any organs of rats in the highest dose group. Macroscopic and microscopic examination of tissues and organs revealed no treatment-related effects. Therefore, under the conditions of the study, the NOAEL for PEG 40 castor oil is determined as 810 mg/kg bw per day based on increased relative liver weight observed in males and females at the dose of 2,050 mg/kg bw per day.

In a 6-month study with dogs, groups of three male and three female beagle dogs were fed twice a day 350 g of a diet containing 0, 10,000, 25,000 or 50,000 mg PEG 40 castor oil/kg, corresponding to approximately 0, 700, 1,750 and 3,500 mg/kg bw per day in males and 0, 833, 2,083 and 4,167 mg/kg bw per day in females. Blood was taken on days 29–31, 84–86 and 126–128, and was analysed for haemoglobin, red blood cell count, haematocrit, white blood cell count, differential leucocyte count, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, leucine aminopeptidase, urea, creatinine, glucose, total protein, cholesterol, total lipids, albumin and sugar. Urine was collected on days 21–22, 78–79 and 169–170, and was analysed for specific gravity, protein, glucose, urobilinogen, sediment and pH. All animals were killed on day 180 and were necropsied. Organs were weighed and subject to histopathology. No effects were reported on body weight gain, blood parameters and urinalysis. Absolute and relative (organ/body weight; organ/brain; organ/heart) thyroid weights were reported to be increased in females given 2,083 and 4,167 mg PEG 40 castor oil/kg bw per day, with no dose response relationship, with no gross or microscopical organ lesions observed. Therefore, under the conditions of the study, the NOAEL for PEG 40 castor oil is determined as 833 mg/kg bw per day based on increased relative thyroid weight observed in females dietary exposed to 2,083 and 4,167 mg PEG 40 castor oil/kg bw per day.

3.2.2.3. Developmental toxicity studies

A developmental toxicity study was performed in NMRI mice. PEG 40 castor oil was administered on gestation days 6–15 to groups of 26–38 pregnant mice at gavage doses of 0, 0 (two untreated control groups), 5,000 or 10,000 mg/kg bw per day. The results were reported in a descriptive way, no

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16 Technical dossier/Section III/Annex III.2.23 and Annex III.2.24.
17 Technical dossier/Section III/Annex III.2.29.
18 Technical dossier/Section III/Annex III.2.30.
tabular data were available. No signs of toxicity were seen during treatment other than slight diarrhoea in some animals. One dam spontaneously gave birth prematurely on day 18. All mice were killed on gestation day 18. The numbers of implantations and resorptions were similar in control and treated groups. There were no effects on fetal weight, fetal length and placental weight. No treatment-related skeletal malformations/anomalies were reported. Examination of the fetuses by transverse sections revealed no treatment-related abnormalities. The top dose level of 10,000 mg/kg bw per day was regarded as the NOAEL for this study.

A rat developmental study was performed using dietary concentrations of 0, 0 (two untreated control groups), 50,000 or 100,000 mg PEG 40 castor oil/kg diet, fed to groups of 24–27 pregnant Sprague–Dawley rats on gestation days 0–20. No signs of toxicity were seen during treatment other than loose stools in the top dose group. No alterations were reported from necropsy of the dams. There were no effects on fetal weight, fetal length and placental weight. No treatment-related skeletal malformations/anomalies were reported. Examination of the fetuses by sectioning revealed no treatment-related abnormalities. The top dietary level of 100,000 mg/kg diet did not show any adverse effect.

3.2.2.4. Other studies

Several in vitro studies have demonstrated that many surfactants, including PEG castor oils, are capable of improving the absorption of ATP-binding cassette transporter substrates (mainly drugs) by interacting with efflux transporters, such as P-gp, MRP2 and BCRP (Hanke et al., 2010). PEG castor oil seems to interact with different carriers and transporters, including solute carriers involved in the absorption of amino acids, vitamins, divalent metal cations and short-chain fatty acids (Al-Ali et al., 2019). A single oral administration of 1 or 5 mg PEG castor oil/kg bw to rats showed to increase both Cmax and AUC of a flavonoid (scutellarin) thereby enhancing its oral bioavailability up to 60% (at the highest dose) (Xiao et al., 2016).

3.2.2.5. Conclusions on toxicology

The additive PEG castor oil did not show genotoxic effects in vitro and in vivo studies. Developmental studies in mice and rats give no indication of adverse effects. Repeated dose toxicity studies showed adverse effects in mice, rats and dogs only at high doses. The lowest NOAEL from the repeated dose studies is 810 mg/kg bw per day based on increased relative liver weight in male rats at the dose of 2,050 mg/kg bw.

3.2.3. Safety for the target species

To support the safety of PEG castor oil in target species, the applicant provided a tolerance study with veal calves, with the animals receiving the additive under assessment via the milk replacer, and a tolerance study with juvenile rainbow trout. However, both studies were not considered, as, in the study with veal calves, high mortality and extensive illness frequency (in pulmonary and gastrointestinal system) in all treatments with subsequent veterinary interventions were reported, as well as no haematology/biochemistry was determined. In the study with juvenile rainbow trout, the raw data and statistical output were not reported, the gross pathology parameters (liver, spleen, fins) examined were limited, as well as no haematology was determined.

As an alternative, the maximum feed concentration which can be considered safe for the target animals can be derived from the lowest NOAEL identified, if suitable data are available (EFSA FEEDAP Panel, 2017c).

Toxicological data were available for PEG castor oil (see Section 3.2.2), for which the lowest NOAEL of 810 mg/kg bw per day was derived from a 6-month study in rats based on increased relative liver weight at the dose of 2,050 mg/kg bw. Applying an uncertainty factor (UF) of 100 to the NOAEL of 810 mg/kg bw per day, the maximum safe intake for the target species was derived for the additive, following the EFSA Guidance on the assessment of the safety of feed additives for the target species (EFSA FEEDAP Panel, 2017c), and thus, the maximum safe feed concentration was calculated (see Table 1).
For dogs, a 6-month repeated dose study was available (see Section 3.2.2.2.3). From this study, an NOAEL of 833 mg/kg bw per day was derived. Applying an uncertainty factor (UF) of 10 to cover intraspecies variability, the maximum safe concentration in feed for dogs was calculated, using as default value for body weight of 15 kg and for feed intake of 250 g DM/day. The calculated maximum safe concentrations in feed for dog are 4,400 mg/kg complete feed.

### 3.2.3.1. Conclusions on the safety for the target species

The FEEDAP Panel concludes that PEG castor oil is safe at a maximum concentration in complete feed of 90 mg/kg for chickens for fattening and other minor growing poultry, 134 mg/kg for laying hens and other laying/breeding birds kept for egg production/reproduction, 121 mg/kg for turkeys for fattening, 162 mg/kg for piglets and other minor growing Suidae, 194 mg/kg for pigs for fattening, 236 mg/kg for sows other minor reproductive Suidae, 231 mg/kg for dairy cows and other dairy ruminants (other than sheep/goats), 142 mg/kg in rabbits and 377 mg/kg in veal calves, 356 mg/kg for cattle for fattening and other growing ruminants, sheep, goat, horses and cats, 4,400 mg/kg for dogs, 407 mg/kg for salmonids and other fin fish and 1,584 mg/kg for ornamental fish. For other species, the additive is considered safe at 90 mg/kg complete feed.

### 3.2.4. Safety for the consumer

Due to the metabolism of PEG castor oil at the intestinal level, no residues of the unchanged additive would be present in target animal tissues and products. The main intestinal metabolites, i.e. polyoxyethylene glycerol and polyoxyethylene (hydroxyl) ricinoleate, are absorbed to a limited extent and not further metabolised, only trace amounts would be found in tissues. Castor oil’s fatty acids will enter the normal metabolic pathways of fatty acids (β-oxidation and limited epoxidation). Therefore, the consumption of tissues and products from target animals given the maximum concentration of PEG castor oil in complete feeds considered safe for the target species would not significantly contribute to consumer exposure to residues of the additive or its metabolites. The FEEDAP Panel concludes that the use of PEG castor oil as feed additive for all animal species would be of no concern for the consumer.

### 3.2.5. Safety for the user

No inhalation toxicity studies were provided. Inhalation exposure is considered unlikely as PEG castor oil is available in form of liquid or wax-like semisolid, which will not form a dust.

### Table 1: Maximum safe concentration in feed for PEG castor oil

| Species                  | Body weight (kg) | Feed intake (g DM/day) | Daily feed intake (g DM/kg bw) | Maximum safe concentration (mg/kg feed) |
|--------------------------|------------------|------------------------|--------------------------------|----------------------------------------|
| Chicken for fattening    | 2                | 158                    | 79                             | 90                                     |
| Laying hen               | 2                | 106                    | 53                             | 134                                    |
| Turkey for fattening     | 3                | 176                    | 59                             | 121                                    |
| Pig for fattening        | 20               | 880                    | 44                             | 162                                    |
| Pig for fattening        | 60               | 2,200                  | 37                             | 194                                    |
| Sow lactating            | 175              | 5,280                  | 30                             | 236                                    |
| Veal calf (milk replacer)| 100              | 1,890                  | 19                             | 377                                    |
| Cattle for fattening     | 400              | 8,000                  | 20                             | 356                                    |
| Dairy cow                | 650              | 20,000                 | 31                             | 231                                    |
| Sheep/goat               | 60               | 1,200                  | 20                             | 356                                    |
| Horse                    | 400              | 8,000                  | 20                             | 356                                    |
| Rabbit                   | 2                | 100                    | 50                             | 142                                    |
| Salmon                   | 0.12             | 2.1                    | 18                             | 407                                    |
| Cat                      | 3                | 60                     | 20                             | 356                                    |
| Ornamental fish           | 0.012            | 0.054                  | 5                              | 1,584                                  |

(a): Complete feed containing 88% dry matter (DM), milk replacer 94.5% DM.

For dogs, a 6-month repeated dose study was available (see Section 3.2.2.2.3). From this study, an NOAEL of 833 mg/kg bw per day was derived. Applying an uncertainty factor (UF) of 10 to cover intraspecies variability, the maximum safe concentration in feed for dogs was calculated, using as default value for body weight of 15 kg and for feed intake of 250 g DM/day. The calculated maximum safe concentrations in feed for dog are 4,400 mg/kg complete feed.
The applicant made reference to studies on skin irritation done using PEG 25, 35 or 40 castor oil applied in rabbits and guinea pigs, and to eye irritation done using PEG 35 castor oil applied to rabbits, and to several studies done in humans. However, the original reports of the studies were not submitted, and therefore, these studies could not be further considered.

In a published study (Tachon et al., 1983), PEG 35 castor oil was tested for allergenic potential injecting the backs of Dunkin–Hartley guinea pigs (10 male, 10 female) with 10 consecutive injections of 0.5 mL PEG 35 castor oil and an occlusive patch applied for 48 h. After 12 days of suspension of the treatment, the animals were challenged by applying 0.5 mL PEG 35 castor oils on the abdomen. At microscopic examination of the macroscopic reactions observed, no indications of sensitisation were observed.

In a skin sensitisation study done according to OECD TG 406, a 50% water solution of PEG 15 castor oil was tested in female albino Hartley–Dunkin guinea pigs. One guinea pig showed a non-conclusive reaction, while no evidence of hypersensitivity was observed in 19 of 20 animals.

In a published study (Goto et al., 2002), the repeated instillation of eye drops containing, among other components, 5% PEG castor oil and 2% castor oil, did not cause eye irritation in 20 patients affected by non-inflamed obstructive meibomian dysfunction when used over 6 weeks.

3.2.5.1. Conclusions on user safety

The FEEDAP Panel considers inhalation exposure of the user unlikely. The Panel is not in the position to conclude on the potential of the additive to be a skin or eye irritant. PEG castor oil is not considered a skin sensitiser.

3.2.6. Safety for the environment

The fatty acids of which castor oil is composed are naturally present in the environment. However, the additive, which includes the polyoxyethylene moiety, is not a natural compound, and therefore, an assessment of the safety for the environment is considered necessary. The applicant provided five studies on biodegradability done according to OECD TG 301b. After 28 days, the biodegradability ranged 66–83%.

Considering that castor oil ethoxylate products are complex mixtures/reaction products of biological materials, they are regarded as unknown or variable composition, complex reaction products or biological materials (UVCB) (ECHA, 2017). Therefore, the studies’ results at 28 days support the identification of the substance as ‘readily biodegradable’ (OECD, 2006). No concern is expected for the environment.

3.2.7. Efficacy

Emulsifiers are substances which promote the formation and stabilisation of an emulsion, which is defined as the result of the dispersion of droplets of one liquid (e.g. fat) in another liquid in which it is not soluble or miscible (e.g. water). To support the efficacy of the additive as an emulsifier, two in vitro studies were provided.

In the first one, a water emulsion of fat-soluble vitamins was prepared with the additive. The suspension contained, in addition to vitamin A, vitamin D3 and vitamin, 160 mL additive/L, 500 mL water/L and 50 mL 1,2-propandiol/L. Samples of the suspension were subject to a visual evaluation and measured for turbidity with a Turbiscan apparatus, which measures fraction of the near-infrared light emitted by the apparatus which is transmitted through the suspension (transmission %), and the fraction which is reflected (backscattering %) along the full length of the glass vessel containing the samples. The suspension was analysed 20 days after mixing and after approximately 5 months. The results showed that, 20 days after mixing, the values of transmission (average: 64.5%) and of backscattering (average: 13.5%) were constant in the whole suspension, indicating the maintenance of the emulsion. The samples measured 5 months after storing showed a comparable pattern of results. Transmission % was increased compared to the initial measurement (72%), indicating an increased solubility, due to further reduction of the emulsion particle size and improved emulsion stability.

To support the efficacy of the additive when used in feedingstuffs (milk replacer), one study was submitted, in which a commercial milk replacer (whey protein, wheat, soya, delactosed whey, pea
protein, premixture, tallow, lard, cocoa fat, palm fat and lecithin; fat content 18%) was supplemented with 30,000 mg additive/kg. A suspension of 60 g milk replacer in 360 g water was prepared, mixing the two components at 1700 rpm for 2 min at 65°C. Samples of the suspension were visually analysed, and subject to Turbiscan measurement immediately after mixing and after 10, 20, 30, 40, 50 and 60 min. The same procedure was followed to analyse samples of the supplemented milk replacer stored in a close container at ambient temperature for 3 months. The results of the analysis of both milk replacer (after manufacturing and after 3 months of storage) showed constant values of backscattering in the vessel, in the range 25–30%, demonstrating the formation of a stable emulsion.

Although the two studies submitted might support the capacity of the additive to stabilise an emulsion of water and non-water-soluble materials over time, the absence of control groups in both the studies, and the lack of evidence in a third feed, do not allow the FEEDAP Panel to conclude on the efficacy of PEG castor oil as an emulsifier.

3.2.7.1. Conclusions on efficacy

The FEEDAP Panel could not conclude on the efficacy of PEG castor oil as an emulsifier in feedingstuffs for all animal species.

4. Conclusions

PEG castor oil is safe at a maximum concentration in complete feed of 90 mg/kg for chickens for fattening and other minor growing poultry, 134 mg/kg for laying hens and other laying/breeding birds kept for egg production/reproduction, 121 mg/kg for turkeys for fattening, 162 mg/kg for piglets and other minor growing Suidae, 194 mg/kg for pigs for fattening, 236 mg/kg for sows other minor reproductive Suidae, 231 mg/kg for dairy cows and other dairy ruminants (other than sheep/goats), 142 mg/kg in rabbits and 377 mg/kg in veal calves, 356 mg/kg for cattle for fattening and other growing ruminants, sheep, goat, horses and cats, 4,400 mg/kg for dogs, 407 mg/kg for salmonids and other fin fish and 1,584 mg/kg for ornamental fish. For other species, the additive is considered safe at 90 mg/kg complete feed.

The use of PEG castor oil as feed additive for all animal species would be of no concern for the consumer.

The FEEDAP Panel considers inhalation exposure of the user to the additive unlikely. PEG castor oil is not considered a skin sensitisier. The Panel is not in the position to conclude on the potential of the additive to be a skin or eye irritant.

The additive is a readily biodegradable substance and is not expected to pose a risk for the environment.

The lack of sufficient data does not allow the FEEDAP Panel to conclude on the efficacy of PEG castor oil as an emulsifier in feedingstuffs.

5. Documentation provided to EFSA/chronology

| Date       | Event                                                                                                                                                                                                 |
|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21/09/2010 | Dossier received by EFSA. Glyceryl polyethyleneglycol ricinoleate (PEG castor oil) for all animal species. Submitted by FEFANA asbl                                                                                                                             |
| 05/12/2012 | Reception mandate from the European Commission                                                                                                                                                      |
| 30/05/2013 | Application validated by EFSA – Start of the scientific assessment                                                                                                                                       |
| 08/10/2013 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: characterisation/safety for the target species |
| 01/03/2016 | Reception of supplementary information from the applicant – Scientific assessment re-started                                                                                                             |
| 02/09/2013 | Comments received from Member States                                                                                                                                                                  |
| 30/09/2013 | Reception of the Evaluation report of the European Union Reference Laboratory for Feed Additives                                                                                                         |
| 05/07/2016 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: safety for the consumer                                |
| 16/06/2017 | Reception of supplementary information from the applicant – Scientific assessment re-started                                                                                                           |
| 13/10/2020 | Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. Issues: safety for the consumer                                |
Glyceryl polyethyleneglycol ricinoleate (PEG castor oil) for all animal species

| Date          | Event                                                                 |
|---------------|----------------------------------------------------------------------|
| 08/12/2021    | Reception of supplementary information from the applicant – Scientific assessment re-started |
| 29/06/2022    | Opinion adopted by the FEEDAP Panel. End of the Scientific assessment |
| 14/07/2022    | Reception of spontaneous information                                  |
| 28/09/2022    | Opinion withdrawn by the FEEDAP Panel                                 |
| 28/09/2022    | Amended opinion adopted by the FEEDAP Panel. End of the Scientific assessment |

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Abbreviations

ANS EFSA Scientific Panel on Additives and Nutrient Sources added to Food

BW body weight

CAS Chemical Abstracts Service

CFU colony-forming unit

DM dry matter

EMA European Medicines Agency

EUROL European Union Reference Laboratory

FAO Food Agricultural Organisation

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

JECFA The Joint FAO/WHO Expert Committee on Food Additives

LOD limit of detection

LOQ limit of quantification

NOAEL no observed adverse effect level

OECD Organisation for Economic Co-operation and Development

UF uncertainty factor

WHO World Health Organisation
Annex A – Executive Summary of the Evaluation Report of the European Union Reference Laboratory for Feed Additives on the Method(s) of the Analysis for Glyceryl polyethylene glycol ricinoleate

In the current application, authorisation is sought under article 10(2) for Glyceryl polyethylene glycol ricinoleate (E 484) under the category/functional group 1(c) ‘technological additives’/‘emulsifiers’ according to Annex I of Regulation (EC) No 1831/2003. The authorisation is sought for the use of the feed additive for all animal species and categories.

Glyceryl polyethylene glycol ricinoleate (E 484) or polyethylene glycol (PEG X) castor oil is obtained by mixing X moles (X from 6.5–200) of ethylene oxide to one mole of castor oil.

The major components formed are the tri-ricinoleate esters of ethoxylated glycerol. The applicant suggested the following technical specification ranges to characterise the feed additive: 16–162 mg KOH/g for the saponification value; 5.5–7.5 for pH; 0–2 mg KOH/g for the acid value and 0–3% wt for the water content.

The feed additive is intended to be incorporated directly into feedingstuffs or through premixtures, with no recommended minimum or maximum concentration levels. However, typical inclusion levels range from 10 to 20 g E 484/kg feedingstuffs.

For the identification of glyceryl polyethylene glycol ricinoleate (PEG X (X = 6.5–200) castor oil) in the feed additive, the applicant proposed several official methods developed by the American Oil Chemists’ Society (AOCS) and the standard of American Society for Testing and Materials (ASTM) for the determination of the: saponification value (AOCS Cd 3–25); acid value (AOCS 3d–63); pH value (ASTM Standard D1172-95:2007) and water content (AOCS Ca 2 e-84). Even though no performance characteristics are provided, the EURL recommends for official control the official AOCS methods and the ASTM standard to identify Glyceryl polyethylene glycol ricinoleate (PEG X castor oil) in the feed additive.

The accurate quantification of Glyceryl polyethylene glycol ricinoleate in premixtures and feedingstuffs is not achievable experimentally. Nevertheless, the applicant presented qualitative data for the identification of the active substance in premixtures and feedingstuffs using nuclear magnetic resonance (NMR). These data do not allow any recommendation by the EURL for official control to quantify Glyceryl polyethylene glycol ricinoleate 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.