Safety of viable embryonated eggs of the whipworm trichuris suis as a novel food pursuant to regulation (eu) 2015/2283

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Safety of viable embryonated eggs of the whipworm *Trichuris suis* as a novel food pursuant to Regulation (EU) 2015/2283

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Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on viable embryonated eggs of the whipworm *Trichuris suis* as a novel food (NF) pursuant to Regulation (EU) 2015/2283. The applicant proposes to use the NF as a food supplement in the format of a 15-mL bottle containing 250 viable embryonated eggs of *T. suis*. The target population for the NF is the general population. Considering the compositional data and proposed conditions of use, the consumption of the NF is considered of no nutritional relevance. Available data suggest that most larvae of *T. suis* after hatching in the intestinal tract of humans remain immature and live for several weeks in the gastrointestinal tract of the human host. Nevertheless, under certain circumstances, *T. suis* can be invasive in human, being able to mature into adult size and reproduce in humans. Human studies have also shown that administration of *T. suis* ova may increase the incidence of adverse gastrointestinal reactions. The Panel considers that there are no studies available that demonstrate the safety of this NF intended for the general population at a proposed intake of 250 viable embryonated eggs of *T. suis* ova per day. Based on the available information, the Panel cannot establish a safe dose at which no safety concerns would be expected. The Panel concludes that the safety of the NF has not been established.

Keywords: *Trichuris suis*, whipworm, embryonated eggs, novel food, safety

Requestor: European Commission following an application by Enteron Science GmbH

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Summary

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on viable embryonated eggs of the whipworm *Trichuris suis* as a novel food (NF) pursuant to Regulation (EU) 2015/2283. The assessment of the safety of this NF, which follows the methodology set out in the EFSA Guidance on the preparation and presentation of an application for authorisation of a NF[1] in the context of Regulation (EU) 2015/2283 and in the Commission Implementing Regulation (EU) 2017/2469, is based on the data supplied in the application, information submitted by the applicant following EFSA's requests for supplementary information and additional information identified by the Panel.

The NF which is the subject of the application are embryonated eggs of the whipworm *T. suis*. The NF is intended to be marketed as a food supplement in the format of a 15-mL bottle containing 250 viable embryonated eggs of *T. suis*. The target population for the NF is the general population.

Considering the compositional data and proposed conditions of use, the consumption of the NF is considered of no nutritional relevance. Available data suggest that most larvae of *T. suis* after hatching in the intestinal tract of humans remain immature and live for several weeks in the gastrointestinal tract of the human host. Nevertheless, under certain circumstances, *T. suis* can be invasive in human, being able to mature into adult size and reproduce in humans. Human studies have also shown that administration of *T. suis* ova may increase the incidence of adverse gastrointestinal reactions.

The Panel considers that there are no studies available that demonstrate the safety of this NF intended for the general population at a proposed intake of 250 viable embryonated eggs of *T. suis* ova per day. Based on the available information, the Panel cannot establish a safe dose at which no safety concerns would be expected. The Panel concludes that the safety of the NF has not been established.

[1] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle H, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Siani A, Sjödin A, Stern M, Tomé D, Vinceti M, Willatts P, Engel K-H, Marchelli R, Pöting A, Poulsen M, Salminen S, Schlatter J, Arcella D, Gelbmann W, de Sesmaisons-Lecarré A, Verhagen H and van Loveren H, 2016. Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. EFSA Journal 2016;14(11):4594, 24 pp. https://doi.org/10.2903/j.efsa.2016.4594

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1. Introduction

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

On 20 July 2018, the company Enteron Science GmbH submitted a request to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283[2] to place viable embryonated eggs of the whipworms (*Trichuris suis*) on the Union market as a novel food.

In accordance with Article 10 (3) of Regulation (EU) 2015/2283, the European Commission asks the European Food Safety Authority to provide a scientific opinion on viable embryonated eggs of whipworm (*Trichuris suis*) as a novel food.

2. Data and methodologies

2.1. Data

The safety assessment of this novel food (NF) is based on data supplied in the application and information submitted by the applicant following an EFSA request for supplementary information.

During the assessment, the Panel identified additional data which were not included in the application.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469.[3]

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application.[1] As indicated in this guidance, it is the duty of the applicant to provide all the available (proprietary, confidential and published) scientific data, including both data in favour and not in favour to supporting the safety of the proposed NF.

This NF application does not include a request for protection of proprietary data in accordance with Article 26 of Regulation (EU) 2015/2283.

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications (EFSA NDA Panel, 2016) and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of the Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only risks that might be associated with consumption of the NF under the proposed conditions of use and is not an assessment of the efficacy of viable embryonated eggs of the whipworm *Trichuris suis* with regard to any claimed benefit.

3. Assessment

3.1. Introduction

The NF which is the subject of the application falls under the category 'food consisting of, isolated from or produced from animals or their parts', as described in Article 3 of Regulation (EU) 2015/2283. This NF is produced by Enteron Science GmbH and consist of viable embryonated eggs of the porcine whipworm *T. suis*. The target population is the general population.

3.2. Identity of the NF

The NF assessed in this application is a non-sterile suspension of the viable embryonated eggs of the whipworm *T. suis*. The whipworm *T. suis* is a nematode commonly present in the caecum and colon of pigs. Adult worm size ranges from 3 to 8 cm with female being larger than male.

[2] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (2013/0435 (COD). OJ L 327, 11.12.2015, p. 1–22).

[3] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

The intended format of the NF is: 250 viable embryonated eggs of *T. suis* suspended in 15 mL of phosphate-buffered solution (pH 2.4) with potassium sorbate as an antimicrobial preservative. Eggs of *T. suis* are oval, of microscopic size (60 × 25 μm), brownish and lemon-shaped with noticeable protruding polar caps at both ends.

The identification of the source organism is performed by reverse transcription polymerase chain reaction (RT-PCR) and is based on a specific sequence region of the ribosomal DNA. The identification method is highly specific for *T. suis* with no relevant homology to other *Trichuris* species or other common parasites in pigs such as *Ascaris suum*, *Oesophagostomum dentatum* and *Hyostrongylus rubidus*.

3.3. Production process

The *T. suis* eggs are produced in minipigs (females, 80–150 days old, of approximately 6–13 kg body weight). Minipigs are inoculated with 2,000 active *T. suis* eggs and following incubation for 49 days, faeces are collected until day 57 post-inoculation. Faeces are then pooled into three fractions (those from days 49 to 51, those from days 52 to 54 and those from days 55 to 57).

Subsequently, eggs are isolated and purified from the faecal pools producing three individual egg suspensions. For each suspension, the egg count is determined, and the yield is calculated. Portions of eggs are taken from each suspension and pooled into one final bulk containing a total of 8 to 19 million eggs. Afterwards, eggs are matured *in vitro* (25°C, 90 days with 0.1 N sulfuric acid at pH 1) to produce viable embryonated eggs. The first 30 days are considered as the inactivation step for viruses by the applicant. Eggs are transferred into a phosphate buffer containing potassium sorbate as preservative. Each batch originates from a group of 2–5 minipigs with an established *T. suis* infection and its traceability is assured.

Finally, suspensions of viable embryonated eggs containing 250 eggs per bottle in 15 mL solution are produced.

The NF is controlled/analysed regarding viral, microbial and parasite contamination. Information on these aspects was provided by the applicant.

3.4. Compositional data

This NF consists of *T. suis* eggs in a phosphate-buffered solution preserved with potassium sorbate. Compositional data were provided by the applicant (Table 1). The shell of the eggs consists of chitin.

Table 1: Composition

Parameter	Result
Protein	< 0.1 g/100 mL
Fat	0.1 g/100 mL
Dry matter	1.7 g/100 mL
Water	99.1 g/100 mL
Ash (minerals)	0.9 g/100 mL
Fibres	< 0.02 g/100 mL
Carbohydrates	0.7 g
Energy value	16 kJ/4 kcal per 100 mL
D-Glucose	< 0.1 g/100 g
D-Fructose	< 0.1 g/100 g
Sucrose	< 0.1 g/100 g
Maltose	< 0.1 g/100 g
Lactose	< 0.1 g/100 g
Total sugars	< 0.1 g/100 g
Salt	0.9 g/100 g
Sodium	370.6 mg/100 g

3.4.1. Stability

The shelf life established by the applicant is linked to the viability of the embryonated eggs. The compositional characteristics of the suspension medium remain stable for at least 12 months when stored at 2–8°C. Under these conditions, the applicant claims that sufficient activity and viability of *T. suis* can be maintained for at least 12 months. The applicant proposes a shelf life of 15 months when stored at 2–8°C.

3.5. Specifications

The applicant assessed potential contaminants of the NF, unwanted accompanying substances, microorganisms, pathogenic viruses and other helminth eggs. According to the applicant, unwanted accompanying substances are removed during the purification step (see Section 3.3). Specifications of the NF proposed by the applicant are indicated in Table 2.

Table 2: Specifications of the NF

Parameter	Specifications	Method of analysis
Appearance of solution	Clear solution. A slight sediment might be visible on standing which disappears completely after shaking	Visual examination
Identity of *Trichuris* species, embryonated	Positive for *Trichuris* species, embryonated (lemon-shaped eggs with a thick shell and transparent protruding polar caps containing a folded larva)	Microscopic determination of morphological characteristics
Identity of *Trichuris suis* species, embryonated	Positive amplification of the *Trichuris suis* ITS2 sequence	RT-PCR of the *Trichuris suis* ITS2 sequence
Potassium sorbate	≥ 0.40 mg/mL equivalent to ≥ 80% of the labelled amount	HPLC
TSO[(a)] inactive (embryonated and non-embryonated)	< 20% (motility index in relation to TSO_{total})	Microscopic determination
Assay TSO_{total} • **TSO 250**	120–495 TSO_{total}/bottle (8–33 TSO_{total}/mL) corresponding to 120–390 TSO_{active}/bottle	Microscopic counting
Potency *in vitro* (TSO active) • **Motility index** • **ATP assay**	≥ 80 % of the eggs contain motile/active larva ≥ 25 nM of ATP is induced by 1,260 (1,120–1,400) eggs (after thermal stimulation)	Microscopic determination Luciferase reaction
Microbiological quality	Total aerobic microbial count ≤ 10^4 CFU/mL Total yeast and mould count ≤ 10^2 CFU/mL *E. coli* Absent (1 mL) Enterobacteria and certain other Gram-negative bacteria ≤ 10^2 CFU/mL *Salmonella* Absent (10 mL) *Staphylococcus aureus* Absent (1 mL)	According to requirements of the pour-plate method and of the test for specific microorganisms

ITS2: internal transcribed spacer 2; RT-PCR: Reverse transcription polymerase chain reaction; HPLC: high-performance liquid chromatography; ATP: adenosine triphosphate; CFU: colony forming units.
(a): *Trichuris suis* ova.

3.6. History of use of the NF and/or of its source

The applicant states that humans have been exposed to *T. suis* eggs from pigs since centuries, in particular farm workers. The applicant states that this NF is commercialised in Thailand.

3.7. Proposed uses and use levels and anticipated intake

3.7.1. Target population

The target population proposed by the applicant is the general population.

3.7.2. Proposed uses and use levels

The applicant intends to market the NF for use as a food supplement in the format of 15 mL bottles containing 250 viable embryonated eggs of *T. suis*.

3.7.3. Anticipated intake of the NF

The applicant proposes an intake of one 15-mL bottle with 250 viable embryonated eggs of *T. suis* per day.

3.8. Nutritional information

Considering the compositional data and proposed conditions of use, the consumption of the NF is considered of no nutritional relevance.

3.9. Safety data

Trichuris suis is a host-specific porcine enteropathogenic parasite in the caecum and colon of affected pigs (Batte et al., 1977).

Potential concerns associated to this NF are related to two aspects: (i) invasiveness/infestation of human by *T. suis*; and (ii) immunological reactions to excretory/secretory peptides. Regarding the immunological reactions, it is known that hatched larvae excrete a group of peptides called excretory/secretory antigens with the aim to survive and persist in the host. These peptides interact with the immune system of the host provoking measurable reactions of the immune system (described further below).

3.9.1. Pathogenicity/invasiveness information

The first studies of potential infections to *T. suis* in human date back to the 1970s. It was reported that *T. suis* larvae are able to transiently colonise humans after administration of single oral doses (1,000 or 5,000 *T. suis* ova) but were eliminated after several weeks of the inoculation. Moreover, no adverse effects were reported (Beer, 1971, 1976). However, a case of invasiveness of *T. suis* in the human host was showed by Kradin et al. (2006) after administration of *T. suis* ova (5 oral doses of 2,500 ova) in a 16-year-old individual with Crohn's disease. The authors reported an iatrogenic *T. suis* infection, characterised by a lymphoplasmatic infiltrate with a substantial number of eosinophil counts consistent with the development of a T helper 2 (Th2)-mediated response, and raised the concern of persistent active infection in humans. Williams et al. (2017) investigated the pathogenicity and immune response developed following the administration of *T. suis* in a healthy volunteer. The authors reported that *T. suis* is able to colonise the human colon, to mature to adult size and to reproduce in humans. Furthermore, genetic analysis of whipworms obtained from the faeces of 12 schoolchildren in Uganda identified one isolate as *T. suis* and two other isolates which showed genetic characteristics of the porcine and human whipworm (Nissen et al., 2012). Finally, infection of humans with *T. suis* has recently been studied in populations in Thailand by molecular techniques where *T. suis* was identified in one out of 27 faecal samples analysed. The authors raised awareness of a zoonotic potential of *T. suis* in Thailand (Phosuk et al., 2018).

Beer (1973) indicated that *T. suis* might provoke epithelial damage favouring other secondary pathogenic infections in piglets. A life-threatening *Campylobacter jejuni* colitis, associated with concomitant human whipworm ova in faeces, was reported in a human case report (Shin et al., 2004). These authors suggested that excretory/secretory products (e.g. proteases and glycoproteins) of whipworms could induce epithelial damage promoting *Campylobacter* attachment.

While Hsu et al. (2005) also raised concerns about the fate of *T. suis* ova; they proposed to provide anti-helminth agents after completion of trials with *T. suis*. According to information provided by the applicant, attention should be directed to an increased risk of microbial or other superinfection in patients treated with *T. suis*. Also, the applicant argued that if symptoms should occur, the causative agent could be treated with anti-helminthic drugs.

3.9.2. Toxicological information

3.9.2.1. Animal data

The main animal studies presented by the applicant were: single dose toxicity studies in monkeys and rabbits (up to 25,000 *T. suis* ova/kg body weight (bw) in monkey and up to 33,000 *T. suis* ova/kg

bw in rabbits); subchronic repeated dose toxicity studies in monkeys (a 7-week study using two animals per gender per group administered once weekly placebo, 500 *T. suis* ova/kg bw or 1,000 *T. suis* ova/kg bw; and a 13-week study using six animals per gender per group administered every two weeks placebo, 500 *T. suis* ova/kg bw or 2,500 *T. suis* ova/kg bw); and a reproductive/developmental toxicity study in rabbits (24 animals per group and gender administered every two weeks during pre-mating and the mating period doses of 500, 2,500 and 7,500 *T. suis* ova/animal while, during gestation, females were dosed weekly).

The applicant considered that rabbits and monkeys were relevant models for toxicity studies in this application. This is because they are non-natural hosts susceptible to a transient colonisation. Rats were identified as not susceptible to infection. The monkey is considered the most relevant model for *T. suis* for the safety assessment in human, while rabbit was mainly selected for the reproductive/developmental toxicity studies.

The main findings reported by the applicant were transient colonisation restricted to the mucosa of the caecum and colon in treatment groups of rabbits and monkeys where focal alterations were occasionally observed. No migration of *T. suis* into other tissues was described by the applicant. The host reaction was dominated by an increase in eosinophils in blood and infiltration of eosinophils in the mucosa of caecum and colon. The applicant referred to the formation of specific immunoglobulin G (IgG) antibodies against *T. suis* and an increased expression of Th2 cytokines in activated mononuclear cells of the peripheral blood and intestinal tissue. No diarrhoea or blood in stool was reported. In the subchronic study in monkeys, the applicant also reported that 'in the male animals of the high dose group on day 40 of treatment showed a tendency to softened faeces was noted'. In relation to the reproductive/developmental studies, the applicant reported that administration of *T. suis* ova provoked no effect on fertility and embryo-fetal development and it showed no teratogenic properties.

EFSA requested full study reports of the 13-week repeated dose toxicity study in monkeys and of the reproductive/developmental toxicity study in rabbits, but these were not made available to EFSA.

In addition, the Panel considered other animal studies available in the literature. Leonardi et al. (2017) investigated the safety of *T. suis* in an immunocompetent and immunosuppressed host (using a rabbit model of dextran sodium sulfate-induced colitis). The authors showed that *T. suis* aggravate colitis in immunocompromised groups of rabbits receiving cyclosporine and methylprednisolone.

Other studies investigating the immunomodulatory effects of the excretory/secretory products of *T. suis* were referred to by the applicant or identified by EFSA (Parthasarathya and Mansfield, 2005; Ebner et al., 2014; Hansen et al., 2017; Laan et al., 2017; Leroux et al., 2018). The evidence available suggests an interaction between *T. suis* and the hosts' immune systems towards the promotion of a modified Th2 immune response. These studies were oriented at studying modulation of immune responses. The Panel notes that these studies were not designed to assess potential adverse consequences of exposure to the excretory/secretory products of *T. suis*.

3.9.2.2. Human data

Information on clinical trials in the original dossier mainly focused on the efficacy of the *T. suis* ova. These studies included trials involving individuals suffering from inflammatory bowel disease (Summers et al., 2003, 2005a,b; Elliott et al., 2005), multiple sclerosis (Flemming et al., 2009) and allergic rhinitis (Bager et al., 2010). No clinical trials have been performed in healthy individuals including children.

In addition to the studies referred to by the applicant, the Panel identified a number of additional studies in the literature that are also described below.

Bager et al. (2010) performed a randomised, double-blind, placebo-controlled clinical trial in 100 individuals with allergic rhinitis allocated to ingest either 8 doses with 2500 live *T. suis* ova or placebo (a dose every 3 weeks). The authors reported a transient diarrhoea peaking at day 41 in 33% of the group treated with *T. suis* compared to the 2% in the placebo group. Upper abdominal pain in the *T. suis* group was 37% vs 4% in placebo and flatulence 43% vs 17% being significantly more frequent in the *T. suis* ova group. According to the authors, superficial damage to the intestinal mucosa by *T. suis* larvae after hatching could be the reason of such clinical observation. An immunologic response due to the infection, i.e. increased eosinophil counts and increased immunoglobulin E (IgE), IgG, IgG_4 and immunoglobulin A (IgA) against *T. suis,* was also observed. The authors concluded that the treatment with *T. suis* induced a clinical and immunological response and a high prevalence of adverse gastrointestinal reactions. In 2011, Bager et al. described in detail the data on the adverse events and the analyses of the gastrointestinal reactions. The authors concluded that the repeated ingestions caused reactions lasting for two weeks. In addition, four months of treatment with *T. suis* provoked a 3- to 19-fold increased rate of incidents with flatulence, diarrhoea and abdominal pain.

The potential use of helminths for the treatment of inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) was investigated by Summers et al. (2003). In this open trial study, seven individuals with either ulcerative colitis or Crohn's disease were administered a single dose of 2,500 *T. suis* ova and followed biweekly for 12 weeks. In the same study, four individuals received 2,500 ova every 3 weeks following the same evaluation scheme. No adverse effects were reported. In an additional study, 29 individuals with active Crohn's disease ingested 2,500 *T. suis* ova every 3 weeks for 24 weeks and this was considered as safe for subjects suffering from Crohn's disease by the authors (Summers et al., 2005a). Subsequently, a randomised, double-blind, placebo-controlled trial with 54 individuals suffering from active colitis were given 2,500 *T. suis* ova or placebo biweekly for 12 weeks. The treatment was reported not to induce side effects (Summers et al., 2005b). The authors stated that adverse events are likely to be rare, and if symptoms would occur, the agent can be easily treated with a readily available anthelminthic. This study also included a crossover phase where individuals on placebo were switched to *T. suis* and those on *T. suis* to placebo for another 12 weeks with no adverse effects observed (Elliott et al., 2005). Sandborn et al. (2013) considered the safety of *T. suis* ova in 36 individuals suffering from Crohn's disease and receiving a single dose of the helminths and no relevant side effects were reported. The authors of this study highlighted the challenge of this type of studies with embryonated *T. suis* eggs in individuals suffering from an inflammatory bowel disease, and whether to assign gastrointestinal symptoms to the treatment with *T. suis* or to the underlying disease. Schölmerich et al. (2017) reported that dosing 250, 2,500 and 7,500 of *T. suis* ova biweekly over 12 weeks did not provoke adverse effects. Similarly to other studies (Bager et al., 2010, 2011; Flemming et al., 2011), Schoelmerich and collaborators suggested that adverse effects are not likely to be observed in this type of studies because of an overlap of effects of *T. suis* with symptoms related to the underlying disease in the individuals tested.

Flemming et al. (2011) reported gastrointestinal side effects following *T. suis* ova treatment. Three of the five individuals suffering from multiple sclerosis treated with *T. suis* reported mild intestinal symptoms. Similar experiments were performed by Benzel et al. (2012) where four individuals were administered 2,500 *T. suis* ova biweekly during 6 months for the treatment of multiple sclerosis. The authors reported that the treatment was well tolerated with no side-effect except for mild gastrointestinal symptoms in one patient likely related to the *T. suis* treatment. Furthermore, Voldsgaard et al. (2015) evaluated the safety and efficacy of 2,500 *T. suis* ova administered biweekly for 12 weeks to 10 individuals with multiple sclerosis. The treatment was well-tolerated with mild and self-limiting gastrointestinal symptoms.

The Panel considers that the uncontrolled studies enrolling small numbers of subjects are not suitable for the assessment of this NF (Flemming et al., 2011; Benzel et al., 2012; Voldsgaard et al., 2015). The Panel also notes that studies with patients suffering from inflammatory bowel disease (Summers et al., 2003, 2005a,b; Elliott et al., 2005) have inherent limitations for their use in the safety assessment of a viable intestinal parasite.

3.9.3. Allergenicity

Bager et al. (2010) noted specific IgE production in humans exposed to 8 doses of 2,500 viable *T. suis* eggs in a human study. No other studies addressing potential adverse effects linked to the allergen capacity of the NF were provided by the applicant. In addition, no studies on cross-reactivity between *T. suis* and known allergens were identified.

4. Discussion

Several studies have investigated the immunomodulatory capacity of the excretory/secretory proteins of *T. suis* to modulate their host's immune system in order to survive and persist. Available data suggest that most larvae of *T. suis* after hatching remain immature and live for several weeks in the gastrointestinal tract of the human host, but they occasionally can develop into adult worms. Case reports in the literature showed that under certain circumstances, *T. suis* is invasive in humans and can mature to adult size and reproduce in humans. The potential infection of humans with *T. suis* has been confirmed in populations in Uganda and Thailand.

Available human studies mainly investigated potential effects of viable *T. suis* in individuals suffering from allergic rhinitis, inflammatory bowel disease or multiple sclerosis. Several of these studies were uncontrolled and enrolled only a low number of subjects. The Panel also considers that studies with patients suffering from inflammatory bowel disease have inherent limitations mainly because of an overlap of effects of *T. suis* with symptoms related to the disease in the individuals tested and are not suitable to demonstrate the safety of this NF.

One randomised, double-blind, placebo-controlled clinical trial in 100 individuals with allergic rhinitis and receiving 8 doses of 2,500 embryonated *T. suis* eggs (a dose every 3 weeks) or placebo reported a significantly increased incidence of diarrhoea, abdominal pain and flatulence in the *T. suis* group versus the placebo group. Repeated intake of embryonated *T. suis* eggs caused reactions lasting for two weeks. In addition, the authors reported that four months of treatment with *T. suis* caused in total, a 3- to 19-fold increased rate of episodes with flatulence, diarrhoea and abdominal pain.

The Panel notes that the intake proposed by the applicant is 250 viable embryonated eggs of *T. suis* ova per day, i.e. lower levels than those at which gastrointestinal effects in that randomised controlled trial were observed. However, the Panel considers that there are no data available which would allow to conclude that the reported gastrointestinal effects when dosing 2,500 eggs would not occur at the proposed intake of 250 eggs per day.

5. Conclusions

The Panel concludes that the safety of the NF has not been established.

Steps taken by EFSA

1) Letter from the European Commission to EFSA with the request for a scientific opinion on the safety of viable embryonated eggs of the whipworm (*Trichuris suis*) as a novel food. Ref. Ares(2018)5333065, dated 17 October 2018.
2) On 17 October 2018, EFSA received a valid application from the European Commission on viable embryonated eggs of the whipworm (*Trichuris suis*) as a novel food, which was submitted by the company Enteron Science GmbH, and the scientific evaluation procedure started.
3) On 5 March 2019, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 6 May 2019, additional information was provided by the applicant and the scientific evaluation was restarted.
5) During its meeting on 2 July 2019, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of viable embryonated eggs of the whipworm (*Trichuris suis*) as a novel food pursuant to Regulation (EU) 2015/2283.

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Abbreviations

ATP	adenosine triphosphate
bw	body weight
CFU	colony forming units
HPLC	high-performance liquid chromatography
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
ITS2	internal transcribed spacer 2

LOD	limit of detection
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	Novel Food
RT-PCR	reverse transcription polymerase chain reaction
Th	T helper
TSO	*Trichuris suis* ova