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Choline and contribution to normal liver function of the foetus and exclusively breastfed infants: evaluation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006

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Abstract

Following an application from Procter & Gamble BV pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to choline and contribution to normal liver function of the foetus and exclusively breastfed infant. The scope of the application was proposed to fall under a health claim referring to children's development and health. The Panel considers that choline is sufficiently characterised. The claimed effect proposed by the applicant is contribution 'to normal foetal and infant development, especially liver'. The proposed target population is 'unborn fetuses and breastfed infants'. Choline is involved in the structure of cell membranes, cell signalling, metabolism and transport of lipids and cholesterol and neurotransmitter synthesis. Although choline can be synthesised de novo by the human body, depletion-repletion studies in humans show that low choline intake leads to liver dysfunction and muscle damage, which are reverted by the administration of dietary choline. For these functions, de novo synthesis of choline by the human body is insufficient and choline must be obtained from dietary sources. No human studies have addressed the effect of low maternal dietary choline intake on liver function in the fetus or exclusively breastfed infants. However, the Panel considers that the biological role of choline in normal liver function and dietary choline being essential for the function applies to all ages, including fetus and infants. The Panel concludes that a cause and effect relationship has been established between the intake of choline by pregnant and lactating women and contribution to normal liver function of the fetus and exclusively breastfed infants.

Keywords: choline, fetal development, health claims, infants, fetus

Requestor: Competent Authority of Belgium following an application by The Procter & Gamble BV

Question number: EFSA-Q-2021-00543

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1. Introduction

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

Regulation (EC) No 1924/2006 harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14–17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims. According to this Regulation, an application shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to choline and contribution to normal fetal and infant development.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of choline, a positive assessment of its safety, or a decision on whether choline is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

Information provided by the applicant

See also section Steps taken by EFSA at the end of this opinion.

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is choline.

Health relationship as claimed by the applicant

According to the applicant, the health effect is related to the 'normal development of the foetus and the breastfed infant, especially of the liver'.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

The applicant claims that 'Insufficient choline intake can cause fat accumulation in the liver mainly through two key mechanisms (1) insufficient phospholipids (i.e. phosphatidylcholine) that are responsible for transporting triglycerides out of the liver via their role as structural components in very low-density lipoprotein (VLDL); (2) choline (via betaine) is a methyl donor. Methyl groups are needed for de-novo synthesis of phosphatidylcholine from phosphatidylethanolamine via phosphatidylethanolamine N-methyltransferase (PEMT)'. 'This PEMT pathway constitutes a source of de-novo choline synthesis. But this source is not sufficient to maintain normal liver function without having a dietary source of choline.'

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'Maternal choline intake during pregnancy and lactation contributes to normal foetal and infant development, especially of the liver'.

Specific conditions of use as proposed by the applicant

According to the applicant, the target populations for the claimed effect are 'unborn foetuses and breastfed infants'. The applicant stated that sources of choline will come from 'food supplements as single ingredient or in multivitamin / mineral combination in an oral form such as tablets or capsules'. According to the applicant, 'there is a gap in supply of choline during pregnancy and lactation of ~ 100 mg/day that needs to be achieved via additional intake, through the natural diet or a supplemental source of choline. These amounts are also aligned with other claims based on essential nutrients, where the claim may be used only for food which is at least a source of choline. Such minimum amounts could be derived with 15% from the adequate intake levels of choline corresponding to 72 and 78 mg/day choline for pregnancy and lactation, respectively.'

Data provided by the applicant

The health claim application on choline pursuant to Article 14 of Regulation (EC) No 1924/2006, was presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims (EFSA NDA Panel, 2021b).

As outlined in the General guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a), it is the responsibility of the applicant to provide the totality of the available evidence.

The application contains data claimed as confidential: analytical tests characterising Choline Bitartrate, manufacturing process, stability information (shelf life).

The application does not contain data claimed as proprietary.

No confidential data from the application was used in this assessment.

2.2. Methodologies

The general approach of the NDA Panel for the evaluation of health claim applications is outlined in the EFSA General guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a).

In assessing each specific food/health relationship, which forms the basis of a health claim, the NDA Panel considers the following key criteria:

i) the food/constituent is defined and characterised;
ii) the claimed effect is based on the essentiality of a nutrient; OR the claimed effect is defined and is a beneficial physiological effect for the target population and can be measured *in vivo* in humans;
iii) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three criteria needs to be assessed by the NDA Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of criterion (i) and/or (ii) precludes the scientific assessment of criterion (iii).

The applicant proposed that this claim is based on the essentiality of nutrients. For the scientific substantiation of claims based on the essentiality of nutrients, the Panel considers the following well-established scientific principles:

i) the nutrient is required for normal human body function(s), i.e. it has an essential mechanistic role in a metabolic function and/or it has the ability to reverse clinical signs and symptoms of its deficiency;
ii) the nutrient cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain normal body function(s);
iii) the nutrient must be obtained from a dietary source.

2.3. Public consultation

In line with EFSA's policy on openness and transparency (EFSA NDA Panel, 2021a), and for EFSA to receive comments from the scientific community and stakeholders, the Application on 'Choline - contribution to normal foetal and infant development, especially of the liver' was released for public consultation from 5 April 2023 to 26 April 2023 (PC-0431). The outcome of the public consultation is described in Appendix A to this Scientific Opinion.

3. Assessment

3.1. Characterisation of the food/constituent

The food/constituent proposed by the applicant as the subject of the health claim is choline from all sources. Choline occurs naturally in foods. It is also present in food supplements.

Choline (CAS number 62-49-7) is a quaternary amine. The chemical formula is $C_5H_{15}NO$. Choline is a water-soluble organic compound generally present in food either with a chloride counterion (chloride salt) or bound to an acetyl group (acetylcholine), to a cytidine diphosphate group (citicoline) or, mainly, to a phosphatidyl group (lecithin) as in milk, liver, eggs and peanuts (EFSA NDA Panel, 2011, 2016). In food supplements, choline is mostly present as choline chloride or as phosphatidylcholine, isolated from soy or egg yolk (Wiedeman et al., 2018a). Choline is measurable in foods by established methods.

The Panel considers that the food constituent choline, which is the subject of the health claim, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is contribution to 'normal foetal and infant development, especially of the liver'. It is also stated in the application that the claim is based on choline being an nutrient essential for normal liver function.

The Panel considers that the target population for the claimed effect is the fetus and exclusively breastfed infants, whereas the target population for choline intake is pregnant and lactating women. The reason for this interpretation is that, under these circumstances, the mother is the only source of dietary choline.

The Panel considers that contribution to normal liver function is beneficial for fetal and infant's development and health.

3.3. Scientific substantiation of the claimed effect

Nutritional function of choline as conditionally essential nutrient

Choline is a dietary component that can also be synthesised *de novo* by the human body and has several biological functions, primarily for being a precursor of phosphatidylcholine (PC), acetylcholine (in cholinergic neurons) and betaine (in the liver and kidney).

PC is a structural component of cell membranes; it is involved in cell signalling, and in the metabolism and transport of lipids and cholesterol. PC is the most abundant choline derivative (Ueland, 2011). Choline can be acetylated to acetylcholine, a neurotransmitter with many functions in both central and peripheral nervous systems. In the liver and kidney, choline can be oxidised to betaine, which is an important source of one-carbon units, in particular during folate deficiency, and contributes to the synthesis of the universal methyl-group donor S-adenosylmethionine (EFSA NDA Panel, 2016).

Whether or not choline needs to be obtained from the diet to sustain these body functions, and under which circumstances, has been under discussion. Indeed, in 1993, the Scientific Committee for Food (SCF, 1993) considered that there was no evidence for the need for dietary choline beyond 6 months of age. However, as it was unclear whether young infants depend on exogenous sources of choline, and because choline is an integral component of human milk, the SCF advised on the mandatory addition of choline to infant formula. In 2014, in the Scientific Opinion on the essential composition of infant and follow-on formulae (EFSA NDA Panel, 2014), the NDA Panel proposed a minimum choline content in infant formula of 25 mg/100 kcal.

In 2016, EFSA published a scientific opinion on Dietary Reference Values (DRVs) for choline (EFSA NDA Panel, 2016). DRVs for choline were established for all population groups, including pregnant and lactating women, as new evidence became available in humans suggesting that endogenous choline synthesis may not be sufficient to cover the physiological requirements. Indeed, results from depletion/repletion studies (Zeisel et al., 1991; Kohlmeier et al., 2005; da Costa et al., 2006; Fischer et al., 2007; Niculescu et al., 2007; Fischer et al., 2010) among adults showed that very low dietary choline intake $\leq$ 50 mg choline/70-kg body weight (Bw) per day within 6 weeks of a depletion phase induced liver dysfunction (fatty liver and subsequent non-alcoholic fatty liver disease) and muscle damage, mostly in men and post-menopausal women.

Scientific substantiation of the claim

In 2011, EFSA published a scientific opinion on the substantiation of health claims related to choline and maintenance of normal liver function (EFSA NDA Panel, 2011) The EFSA Panel concluded that 'a cause and effect relationship has been established between the consumption of choline and maintenance of normal liver function'. The target population was the general population.

The applicant performed a literature search in PubMed and Google Scholar using combinations of the following key words: "maternal choline and fetal development", "maternal choline and fetal liver", "maternal choline deficiency and fatty liver", "maternal choline intake and fatty liver", "choline deficiency in pregnancy and fatty liver", "choline deficiency during lactation and fatty liver", "choline and fetal liver", "choline metabolism in the fetus" and "choline deficiency during pregnancy and newborn health". The applicant also added some references identified as relevant to the claim. There was no time limit, but the applicant focussed on earlier studies (1930–1990).

Search was not systematic, and the applicant did not use search field tags nor MeSH terms in PubMed. There were no exclusion/inclusion criteria. The applicant identified 10 narrative reviews, 2 systematic reviews with meta-analyses, 3 depletion-repletion studies in humans, 6 human intervention studies, 24 human observational studies, 44 animal studies and 12 *in vitro* studies as being pertinent to the claim.

The majority of human intervention (including depletion-repletion) studies provided by the applicant as being pertinent to the health claim had been already considered by the NDA Panel in the scientific opinion on DRV for choline (EFSA NDA Panel, 2016), which is taken as the basis for the scientific substantiation of the claim based on the essentiality of nutrients in this opinion. These studies substantiating the contribution of choline to normal liver function are hereby described.

The Panel notes that, among the human studies provided by the applicant that were published after the EFSA DRV opinion on choline, one meta-analysis of five observational studies (Obeid et al., 2022) and one randomised controlled trial (Cho et al., 2020) addressed endpoints other than liver function (e.g. neural tube defects in the offspring, trimethylamine-N-oxide levels), whereas one cohort study (Hagström et al., 2016) and one narrative review (Hagström et al., 2016; Sarkar et al., 2020) reported on non-alcoholic fatty liver disease in pregnant women but not on choline intake. The applicant also provided a series of references reporting on dietary surveys and choline intakes in different population groups (including toddlers, pregnant and lactating women), and on choline concentrations in human milk, mostly in countries outside the EU (Wiedeman et al., 2018b; Sarkar et al., 2020). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect.

Among the depletion/repletion studies available (Zeisel et al., 1991; Kohlmeier et al., 2005; da Costa et al., 2006; Fischer et al., 2007; Niculescu et al., 2007; Fischer et al., 2010), only one study (Fischer et al., 2007) reported the amount of choline needed to replete subjects with signs of organ dysfunction. From the 31 healthy men and 35 healthy women (n = 20 premenopausal and n = 15 postmenopausal) that were initially recruited, 57 (26 men, 16 premenopausal women and 15 postmenopausal women) completed the study. In the per-protocol analyses, age ranged from 18 to 70 years. During the depletion phase with < 50 mg choline/70 kg bw per day (42 days), 77% of male, 80% of postmenopausal female participants and 44% of premenopausal women became choline deficient and developed liver and muscle dysfunction. Signs of liver dysfunction included increase of the ratio of liver fat to spleen fat (hepatic steatosis), increase of serum level of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase activity. Signs of muscle damage included an increase of creatine phosphokinase activity. 26 participants had liver dysfunction alone.

During the repletion phase (3–40 days), participants with organ dysfunction, when fed the low-choline depletion diet, were fed graded increasing intakes of choline for 10 days each until signs of organ dysfunction resolved: 137.5 mg, 275 mg, 412.5 mg and 550 mg per 70 kg per day. In this study, up to about 400 mg choline/70 kg vw per day was sufficient to replete 18 of 25 deficient subjects (70%), who showed signs of choline deficiency after experimental choline depletion, and to reverse their symptoms of organ (liver and muscle) dysfunction. The levels of biomarkers of liver (aspartate aminotransferase and alanine aminotransferase) and muscle (creatine phosphokinase) damage in blood were also normalised. During the depletion phase, serum uric acid concentrations increased in all subjects.

Choline depletion/repletion studies did not provide sufficient data to calculate average requirements (AR) for choline, and thus adequate intakes (AI) for adults were set at 400 mg/day and based on observed intakes (EFSA NDA Panel, 2016). AI for adults were based using the midpoint (370 mg choline/day) of the range of observed mean intakes (ranging from 270 to 470 mg choline/day) in

healthy general populations in Europe and investigated in 12 national surveys undertaken in nine countries in Europe between 2000 and 2011. The AI for pregnant women was calculated by isometric scaling from the AI for non-pregnant women using the mean gestational increase in body weight and set at 480 mg choline/day by considering transfer of choline from mother to the fetus and choline accretion in the fetus. The AI for lactating women was set at 520 mg/day by considering the secretion of choline through breast milk, which during the first 6 months of exclusive breastfeeding is about 120 mg/day (EFSA NDA Panel, 2016).

The Panel also notes that the AI for choline for pregnant and lactating women is derived from the AI for adults, considering additional requirements to support normal growth and development of the fetus and exclusively breastfed infant, for whom the mother is the only source of dietary choline.

No human studies have addressed the effect of low maternal dietary choline intake on liver function in the fetus or exclusively breastfed infants. However, the Panel notes that fat accumulation in the liver and liver dysfunction are among the signs of choline deficiency in humans, suggesting that endogenous synthesis of choline is not sufficient to support liver function in the long term under conditions of low dietary choline intake. The Panel also notes that the scientific basis for the derivation of the AIs for choline for pregnant and lactating women are the same as for adults (signs and symptoms of choline deficiency, including liver dysfunction), and that it is biologically plausible that choline deficiency in the mother could lead to liver dysfunction in the offspring, for which the mother is the only source of dietary choline.

Among the animal studies provided by the applicant as being pertinent to the claim, only one study in rats assessed the impact of maternal choline intake on liver fetal development (Meader, 1965). Pregnant female Long Evans rats (n = 30; 16 weeks of age) were divided into three groups of 10 rats each: one was fed a choline-deficient diet during the 21 days of gestation; one was fed a choline-deficient diet supplemented with 2% choline chloride during the 21 days of gestation; the third group was fed a choline-deficient diet during 30 days prior to and during the 21 days of gestation. Additional two groups of 10 non-pregnant animals each received either a choline supplemented or a choline-deficient diet for 21 days. The amount of stainable fat as assessed in frozen liver samples was higher in pregnant than in non-pregnant rats fed the choline-deficient diet. The quantity of stainable fat present in the livers of the fetuses removed from choline-deficient mothers was directly proportional to the amount of maternal fat in the liver and almost absent in pregnant and non-pregnant animals fed the choline-supplemented diet. The amount of stainable liver fat was also almost absent in fetuses of mothers fed the choline-supplemented diet. The amount of stainable liver fat in the fetuses of mothers fed the choline-deficient diet was high and directly proportional to the duration of the choline-deficient feeding: stainable liver fat was higher in mothers (and their fetuses) fed the choline-deficient diet for 51 days vs mothers (and their fetuses) fed the choline-deficient diet only during pregnancy. No death or developmental defects were identified among these fetuses.

The Panel considers that this study in rats (Meader, 1965) supports the contribution of maternal choline intake to normal liver function of the offspring for which the mother is the only source of dietary choline. The Panel considers that the biological role of choline in normal liver function and dietary choline being essential for the function applies to all ages, including fetus and infants.

The Panel concludes that a cause and effect relationship has been established between the intake of choline by pregnant and lactating women and contribution to normal liver function of the fetus and exclusively breastfed infants.

3.4. Panel's comments on the proposed wording

The Panel considers that the following wording reflects the scientific evidence: 'Maternal choline intake during pregnancy and lactation contributes to normal liver function of the foetus and exclusively breastfed infants'.

3.5. Conditions and restrictions of use

The target population for the claimed effect is the fetus and exclusively breastfed infants, whereas the target population for choline intake is pregnant and lactating women. In order to bear the claim, a food should contribute to dietary choline intake. DRVs (adequate intakes) for choline of 480 and 520 mg/day have been established for pregnant and lactating women, respectively (EFSA NDA Panel, 2016). To date, no tolerable upper intake level (UL) has been set for choline by EFSA but a UL of 3.5 g/day for adults has been put forward by the US Institute of Medicine (IOM).

4. Conclusions

On the basis of the data presented, the Panel concludes that:

- the food constituent, choline, which is the subject of the health claim, is sufficiently characterised.
- the claimed effect proposed by the applicant is 'contribution to normal fetal and infant development, especially of the liver'. The target population proposed by the applicant is 'unborn foetuses and breastfed infants'. The Panel considers that contribution to normal liver function is beneficial for fetal and infant's development and health.
- a cause and effect relationship has been established between the intake of choline by pregnant and lactating women and contribution to normal liver function of the fetus and exclusively breastfed infants.
- the following wording reflects the scientific evidence: 'Maternal choline intake during pregnancy and lactation contributes to normal liver function of the foetus and exclusively breastfed infants'.
- the target population for the claimed effect is the fetus and exclusively breastfed infants, whereas the target population for choline intake is pregnant and lactating women.
- in order to bear the claim, a food should contribute to dietary choline intake. DRVs (adequate intakes) for choline of 480 and 520 mg/day have been established for pregnant and lactating women, respectively (EFSA NDA Panel, 2016). To date, no tolerable upper intake level (UL) has been set for choline by EFSA but a UL of 3.5 g/day for adults has been put forward by the US Institute of Medicine (IOM).

Documentation as provided to EFSA

Health claim application on pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0504_BE, Appian number: HC-2021-1610). Submitted by The Procter & Gamble BV.

Steps taken by EFSA

1) The application was received by EFSA on 28/09/2021. The health claim was initially submitted on 'choline' and 'normal fetal and infant brain development and function'. From the information and data provided in the application, it was unclear whether the health claim was based on the essentiality of nutrients or not.
2) The application was validated on 17/06/2022 and the scientific evaluation started.
3) EFSA sent Additional Data Request (ADR) letter to the Applicant on 13/07/2022. The clock was stopped.
4) On 28 July 2022, a clarification teleconference was held between the applicant and EFSA staff (upon the applicant's request) to clarify the scientific requirements for health claims based and not based on the essentiality of nutrients, as illustrated in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2021a,b). The applicant requested an extension of the deadline to revise the dossier.
5) On 15 September 2022, a follow-up clarification teleconference was held between the applicant and EFSA staff (upon the applicant's request) regarding the proposed claimed effect and the need to revise the dossier on that basis. A further extension of the deadline was requested to re-structure the dossier.
6) On 16 January 2023, the applicant submitted the reply to the ADR letter and the revised dossier. In the revised dossier, the applicant specified that the claim is based on the essentiality of nutrients, acknowledged the role of choline on liver function, and proposed a new wording for the claim: 'Maternal choline intake during pregnancy and lactation contributes to normal foetal and infant development, especially of the liver'. The clock re-started for the scientific evaluation.
7) The updated application on "Choline - contribution to normal fetal and infant development, especially of the liver" was open for public consultation from 05 April 2023 to 26 April 2023 (PC-0431).
8) During its meeting on 22/06/2023, the NDA Panel, having evaluated the data, adopted an opinion on the scientific substantiation of a health claim related to choline and contribution to normal liver function of the foetus and exclusively breastfed infants.

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Abbreviations

ADR	additional data request
AI	adequate intakes
AR	average requirements
bw	body weight
DRV	Dietary Reference Values
IOM	US Institute of Medicine
NDA	Panel on Nutrition, Novel Foods and Food Allergens
PC	phosphatidylcholine
PEMT	phosphatidylethanolamine N-methyltransferase
SCF	scientific Committee for Food
UL	Tolerable Upper Intake Level
VLDL	very low-density lipoprotein

Appendix A – Outcome of the public consultation on the Application on 'Choline - contribution to normal fetal and infant development, especially of the liver' (HC-2021-1610)

One comment was submitted twice by one contributor from Iran. The comment is published on the EFSA web page as received (https://open.efsa.europa.eu/consultations/a0c0900000BoWSjAAN?search=choline).

General comments

Contributor/Organisation	Comment and reply
Veterinary animal feed hygiene (Iran)	**Comment**: 'Choline is part of group B vitamins. Choline is necessary for metabolism and fat metabolism and is used to burn fat in the body. This article is very important. If the amount of choline in the body is too low, excess fat accumulates in the liver. Choline is a water-soluble substance. Choline is not a vitamin or mineral, but it is known as a part of the B vitamins (B complex) and is thought to be the same as vitamin B4. A very small amount of choline is made in the liver, but the body's needs must be met by consuming substances that are among the best sources of choline. Choline plays a very important role in metabolism and fat metabolism; Therefore, it is a substance that is used to burn fat in the body. If its amount in the body is low, excess fat accumulates in the liver and causes fatty liver and obesity. Best Choline Sources: Choline, or vitamin B4, is found in foods such as eggs, meat, fish, chicken and whole grains. Since the daily consumption of choline is necessary for men and women, we explain this vitamin in each food item so that you know the best sources of choline better'. Attachment contains the full commentary, of which only the paragraphs relevant to this opinion appear above as submitted. The remaining parts of the commentary refer to food safety aspects and animal feed, which are out of the scope of the scientific assessment of health claims made on foods. **Reply**: Biological functions and food sources of choline are described in the Scientific Opinion on DRVs for choline (EFSA NDA Panel, 2016), which has been used as a basis for both the characterisation of the food/constituent and the scientific substantiation of the claim in this opinion. No change to the opinion was introduced on the basis of this comment.