



FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

**Systematic review of the evidence for a
relationship between α -linolenic acid (ALA) and
linoleic acid (LA), and normal growth and
development in children**

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Executive Summary

<i>Is dietary intake of α-linolenic (ALA) and linoleic acids (LA) together needed for normal growth and development in children?</i>	
Food-health relationship	Dietary intake of ALA and LA together is needed for normal growth and development in children (aged ≥ 1 to < 18 years)
Proposed degree of certainty (GRADE rating)	Not assessable
Component	Notes
Body of evidence	No suitable randomised controlled trials, case reports, case series or clinical trials examining the effects of deficiency of dietary ALA and LA given together in children related to growth and development were identified and, therefore, none were included in this systematic review.
Consistency	There was no body of evidence to assess from which to draw a conclusion about consistency.
Causality	There was no body of evidence to assess from which to draw a conclusion about causality.
Plausibility	ALA and LA cannot be synthesised by humans and they are both required as precursors to bioactive lipid mediators. It is plausible that dietary deficiency of ALA and LA could influence normal growth and development, either through the role of these fatty acids in cell membranes or as precursors to cellular signalling compounds.
Generalisability	No suitable studies in humans were identified. Therefore, generalisability to food or property of food for consumption by healthy individuals is not applicable.

The effects of dietary deficiency of the fatty acids α -linolenic (ALA) and linoleic acid (LA) and their effects on growth and development in children have been reviewed by FSANZ. The requirements of the *Application Handbook* and of *Schedule 6 – Required elements of a systematic review* in the *Australia New Zealand Food Standards Code* were followed.

Four case studies were identified (Holman et al. 1982a; Heymans et al. 1982; Bjerve et al. 1988; Gura et al. 2005) in which seriously ill children with essential fatty acid deficiency received ALA and LA together as a dietary intervention after which the children’s growth and development were assessed. However, these studies were excluded because the dietary interventions also contained fish oil rich in other polyunsaturated fatty acids (PUFA), the background diet was high in ALA, LA and/or other PUFA, and medications were also administered that can interfere with growth and development.

Due to the lack of suitable studies that investigated whether ALA and LA together are needed for normal growth and development in children, FSANZ regards the food-health relationship that is the subject of this review as being ‘not assessable’.

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1 Introduction

In 2010, the European Union authorised (Commission Regulation (EU) No. 376/2010) the health claim *Essential fatty acids are needed for normal growth and development of children*. The use of this claim requires information be provided to the consumer that *the beneficial effect is obtained with a daily intake of 2 g of α -linolenic acid (ALA) and a daily intake of 10 g of linoleic acid (LA)* (The European Commission 2010).

In examining the evidence to support this claim in the relevant Scientific Opinion, the Panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority (EFSA) concluded that the claim was established based on “case reports documenting clinical signs and symptoms of essential fatty acid deficiency (largely as LA deficiency) in infants and children, one randomised intervention trial on the effects of LA deficiency in infants and two case reports documenting specific ALA deficiency in children 6-7 years of age” (EFSA 2008). The Scientific Opinion covered children aged 1-12 years.

FSANZ notes that EFSA did not carry out a systematic review of the literature to examine the relationship between the consumption of ALA and LA by children and associated effects on normal growth and development. FSANZ also notes that EFSA based its recommendation on an assessment of whether or not LA and ALA are essential dietary nutrients.

FSANZ is considering whether a relationship between intake of ALA and LA and normal growth and development in children can be incorporated into Schedule 4 – Nutrition, health and related claims in the *Australia New Zealand Food Standards Code*. FSANZ considers that “needed for normal” is part of the wording specifications for the EU claim and that the EU claim relates to a deficiency, rather than indicating that increased ALA and LA intake enhances the growth and development of children. Therefore FSANZ carried out a systematic review of the evidence obtained from human studies that dietary ALA and LA is required for normal growth and development in children.

1.1 Food or the property of food

The food or property of food is ALA and LA consumed together in an unspecified ratio. Sources of ALA and LA such as fish, nuts and seeds that contain other ω -3 and ω -6 polyunsaturated fatty acids (PUFAs) are not the subject of this systematic review.

Both ALA and LA are 18 carbon-atom chain fatty acids, differing in the number and positions of their double bonds. In ALA (an ω -3 PUFA) the 3 *cis* double bonds begin at the third carbon atom from the methyl end of the molecule whereas LA (an ω -6 PUFA) has 2 *cis* double bonds beginning at the sixth carbon atom from the methyl end (Nakamura and Nara 2004; Barceló-Coblijn and Murphy 2009). After extraction with an organic solvent and conversion to their corresponding methyl esters, ALA and LA content in food and blood serum or plasma is usually measured by gas chromatography (GC) with flame ionization detection (GC-FID) and, when necessary, with mass spectrometric detection (GC-MS) (Christie 1998; AOAC 2000).

Both ALA and LA are abundant in certain terrestrial plants and their oils such as flaxseed (also known as linseed), rapeseed (some cultivars are known as canola), soybean, chia seeds, olive and tree nuts (Ryan et al. 2007; Dyer et al. 2008; Ayerza and Coates 2011). ALA and LA are also found in animal sources such as poultry eggs, red meat, poultry meat, animal fat and dairy products (FSANZ 2014; Ganesan et al. 2014). These fatty acids are usually present and stored in plants seeds or edible animal tissues mainly as triglycerides or phospholipids (Millar et al. 2000; Voelker and Kinney 2001; Baghurst 2004).

The main food sources of ALA and LA for Australians and New Zealanders are terrestrial plant oils, edible seeds, poultry and red meats as well as dairy products (University of Otago and NZ Ministry of Health 2011; Australian Bureau of Statistics 2014). Mean LA and ALA intakes by Australian children aged 2 to 18 years are 7.7 and 1.1 g/day, respectively (Australian Bureau of Statistics 2014).

Both ALA and LA are precursors to compounds that are important structural components of cell membranes and biochemical processes such as cell signalling. Because humans cannot *de novo* synthesise these two fatty acids, they have to be present in the diet (Barceló-Coblijn and Murphy 2009) and, therefore, are considered to be essential nutrients. There is not enough information available to allow an Estimated Average Requirement (EAR) for ALA or LA to be set. Therefore an Adequate Intake (AI), based on the median intake of the population of Australia and New Zealand, has been set (NHMRC and NZ MoH 2006).

1.2 Health effect

The EU health claim relating to ALA and LA is not specific in defining normal growth and development of children. Therefore, a broad approach was taken in this systematic review.

Child growth can be broadly defined as the change in body size and shape relative to the passage of time (World Health Organization 1995; Cameron 2012a). Growth can include any aspect of changes in external body or anthropometric measurements such as body mass, height or a combination of these measurements as absolute values or in relation to growth charts. In children, the three most commonly used anthropometric indices are weight-for-height, height-for-age, and weight-for-age. These indices can be expressed as Z-scores, percentiles, or percentage of median, which enable comparison of a child or a group of children with a reference population (World Health Organization 1995; de Onis and Blössner 2003; Wang and Chen 2012; Cameron 2012b).

Although growth and development are sometimes considered as one biological process, they are contemporaneous but distinct processes (Cameron 2012a; Rovner and Zemel 2013). Growth is a physical increase in anthropometric measurements with time (Cameron 2012a; Cole 2012) whilst physiological and cognitive development can be linked to biological maturity and increases in functional and behavioural ability (Anderson et al. 2001; Smith et al. 2011; Brown et al. 2012). Biological and functional development can be assessed by monitoring and measuring the progress in several aspects of body morphology and physiology leading to maturity. Skeletal, somatic, sexual, and dental development and maturity assessment by measuring, observing, and quantifying changes over time are frequently used to assess development in children (Mirwald et al. 2002; Malina et al. 2004; WHO Multicentre Growth Reference Study Group 2006). Cognitive and behavioural development in children is assessed mainly by monitoring signs and testing changes of gross and fine motor skills, attention, speech and language learning, social behaviour and developing emotional abilities (Campbell et al. 2001; Goswami 2010; Greco et al. 2011).

1.3 Proposed relationship

The food-health relationship being assessed in this report is:

- Dietary intake of ALA and LA together is needed for normal growth and development in children.

2 Evaluation of evidence

The relationship investigated by FSANZ was that the dietary intake of ALA and LA is needed for normal growth and development of children, rather than an increased intake of ALA and LA enhances growth and development parameters.

FSANZ did not identify an existing systematic review of the effects of correcting diets deficient in ALA and LA on human growth or development. Therefore, a new systematic review was undertaken.

2.1 Methods

2.1.1 Search strategy

Because no definition of normal growth and development was provided in the EFSA opinion relating to the EU-authorized claim, a broad search strategy was designed to retrieve publications about the effects of essential fatty acids on general health and physiological functions in humans. The aim of the search was to identify all health outcomes associated with diets deficient in ALA and LA. Therefore, no specific outcome measures were included in the search.

Searches were conducted in PubMed on 4th March 2015, Cochrane CENTRAL on 3rd March 2015 and EMBASE on 10th March 2015 using the search strategies detailed in Appendix 1. Medical subject heading (MeSH) terms were used to contain the scope of the search results within EMBASE and PubMed. The amount of health outcomes research associated with dietary fatty acids is substantial, with the majority not related to essential fatty acid deficiency. PubMed search results were limited to studies in humans. No date limits were applied to any searches. Eighteen papers were also identified by hand searching the reference lists of the screened articles.

The Australia New Zealand and WHO Clinical Trials Registries were searched on the 28 July 2015 for the text words 'essential fatty acid'. Only one study (ACTRN12610000616077, from 2010, retrospectively registered) was identified as being potentially relevant to FSANZ's review. Although a paper that appears to be the result of the 2010 study (Bauer et al. 2014) was located, the intervention did not consist solely of ALA and LA. Other registered trials that were identified did not include ALA and LA as the intervention, examine the effects of deficiency, or examine growth and development in children. The studies were therefore not included in this review.

To confirm the validity of FSANZ's literature search strategy, the articles retrieved from the search were compared with those cited in the relevant EFSA Scientific Opinion (EFSA 2008), two other Scientific Opinions by EFSA regarding ALA (EFSA 2009; EFSA 2011), documents from the National Health and Medical Research Council (NHMRC), New Zealand Ministry of Health (NHMRC and NZ MoH 2006) and the US Institute of Medicine (IoM 2005) to demonstrate the search strategy had retrieved articles that were cited in the above opinions and documents.

2.1.2 Inclusion and exclusion criteria

Studies to be included were not limited to a particular study design, as relevant information could have been reported in case reports, case series, randomised controlled trials, or other trial designs. Study subjects included children 12 months of age and older but younger than 18 years because *Standard 1.2.7 - Nutrition, health and related claims* of the *Australia New Zealand Food Standards Code* does not permit health claims on formulas intended for

infants under the age of 12 months and a person of 18 years of age is, generally, regarded in Australia and New Zealand to be an adult. The eligibility criteria are summarised in Table 1.

Table 1. PICOTS criteria for study selection

Population	Participants aged 12 months and older but less than 18 years with clinical signs and symptoms of essential fatty acid deficiency.
Intervention	ALA and LA added to dietary intervention or nutrition support.
Comparator	For case reports and series, comparator is the same individual before ALA and LA intervention was initiated. For clinical trials, comparator is participants who continued on a diet free of ALA, LA and other PUFA
Outcome	All reported signs and parameters related to growth and development.
Time	No limits.
Study design	Randomised controlled trials, clinical trials, case series or case reports.

Studies using mixtures of fatty acids that included ALA and LA, but no other PUFA as the intervention, compared to a control group receiving the same mixture of fatty acids not containing ALA and LA or any other PUFA, were included because the treatment effects could be attributed to the ALA and LA intervention.

Intervention with both ALA and LA could be given in various ways, including as fatty acids or oil emulsions added to parenteral or enteral intervention. To be eligible for inclusion, studies must have included both a PUFA-free (or negligible PUFA) phase and a phase where both ALA and LA were added to the baseline diet. Studies in which changes in growth and development parameters linked to PUFA deficiency were reported, but no ALA and LA was administered to address these symptoms were excluded. To be included studies must have provided information on clinical measures relevant to growth and development in the study participants.

The literature search for this review was carried out as part of a broader search for studies of dietary fatty acid deficiency and any health outcomes. From this broad search, relevant studies in children where growth or developmental outcomes were associated with diets deficient in lipids were identified.

In order to find studies, no minimum duration was set. However, it was recognised that duration would be an important factor to assess when reviewing studies as some months of follow-up would be needed to assess growth. The length of time would depend on child age because growth occurs at different rates at different ages. Therefore a study of short duration is less likely to find an effect on growth.

2.1.3 Exclusion criteria

The following exclusion criteria were established:

- Studies in which the reported outcome was only comprised of changes in plasma or serum lipid or ALA and LA profile, without accompanying changes in parameters related to growth and development.
- Subjects receiving ALA and LA with medical treatments that could potentially interfere with growth and development.
- Subjects receiving ALA and LA concurrent with other PUFA interventions.
- Subjects who did not have clear clinical signs or symptoms of essential fatty acid deficiency before the initiation of ALA and LA intervention.
- Diets that contained substantial amounts of ALA, LA or other PUFA intake before the intervention phase.
- Studies involving enhanced intake, i.e. above the normal dietary intakes in healthy populations.

2.1.4 Study selection, data extraction and quality assessment

Records identified during the search process were imported into EPPI-Reviewer 4 (<http://eppi.ioe.ac.uk/cms/er4>). Following the removal of duplicates, records were screened on title and abstract. Identified full-text articles were retrieved and assessed against the inclusion/exclusion criteria. Screening was conducted by two investigators.

As no studies were found, no data extraction or quality assessment was done of individual studies (Higgins and Green 2011) or the body of evidence (Guyatt et al. 2008; Guyatt et al. 2011).

2.1.5 Statistical analyses

Neither meta-analysis nor any other statistical analysis of data was undertaken as no studies were included in the systematic review.

2.1.6 Subgroup analyses

No sub-group analyses were conducted.

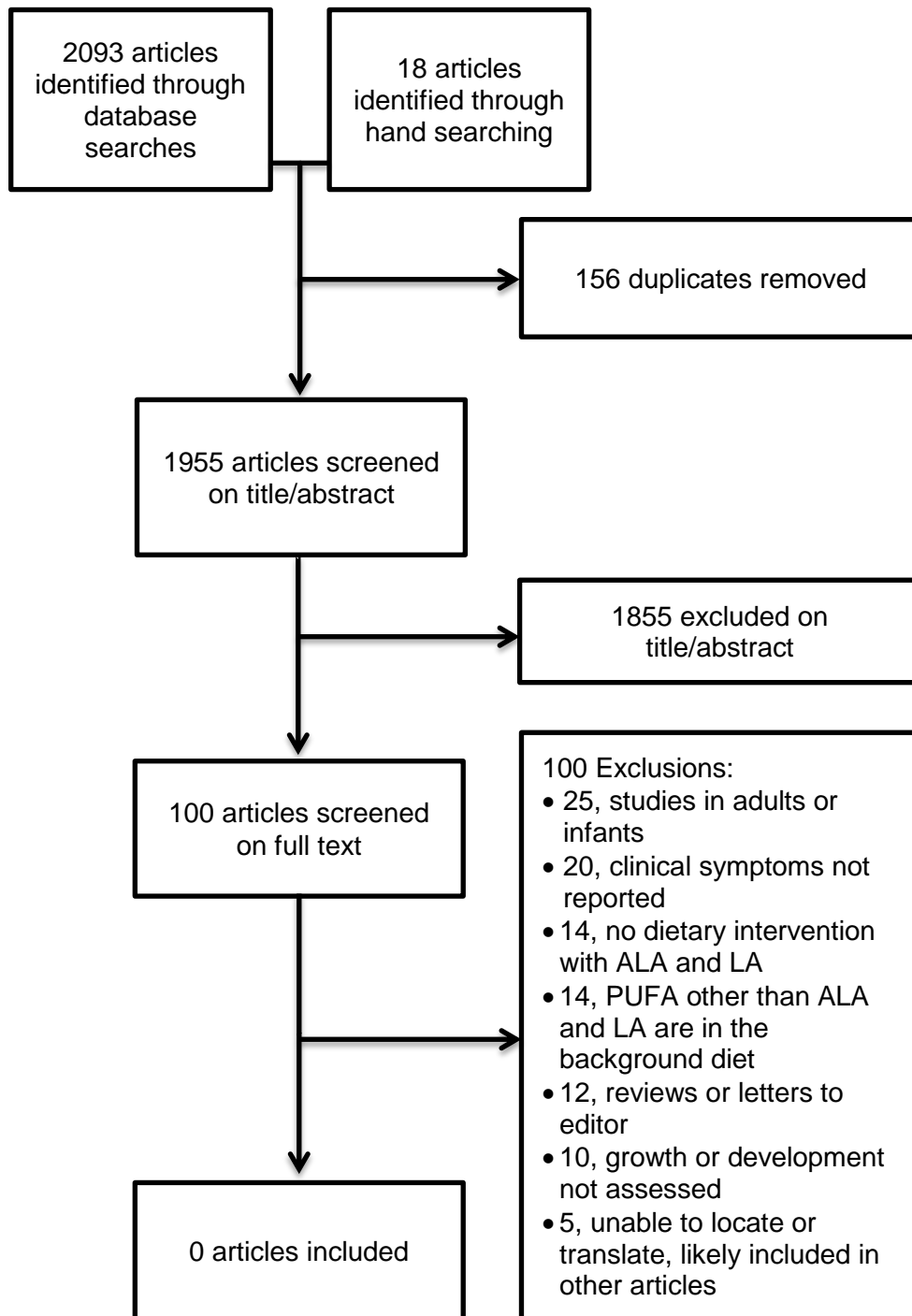


Figure 1: PRISMA diagram of study identification process

2.2 Results

2.2.1 Search results

The screening of articles retrieved from the search strategies is detailed below (Figure 1). Studies excluded after full-text screening are also listed (Appendix 2).

2.2.2 Included studies

There were 100 studies screened on full text, of which four studies were found (Holman et al. 1982a; Heymans et al. 1982; Bjerve et al. 1988; Gura et al. 2005) reporting on seriously ill children who received ALA and LA within a dietary intervention and had their growth and development assessed after the intervention. However, the studies were not included in the systematic review because the interventions contained either other PUFA (from fish oil), the background diet was high in ALA, LA and/or other PUFA or the patients received medications that can interfere with growth and development. Therefore, there were no studies meeting the PICOTS inclusion criteria.

2.2.3 Quality assessment of studies

As there were no studies that met the inclusion criteria in this systematic review no individual or overall quality assessment of studies was performed. Similarly, publication bias could not be assessed.

2.3 Summary of evidence

2.3.1 ALA and LA in normal growth and development in children

There were no studies identified that used ALA and LA as a dietary or nutritional intervention in children and assessed any aspect of normal growth and development following the intervention. Therefore, there is no evidence to be assessed.

3 Weight of evidence

Of the 100 articles screened on full text, no studies were identified that met the inclusion criteria. Therefore, no relevant evidence derived from human studies was identified that could be used to substantiate a relationship between the intake of ALA and LA as being needed for normal growth and development of children.

3.1 Assessment of body of evidence

3.1.1 Consistency of relationship

Not assessed due to the absence of evidence.

3.1.2 Causality

Not assessed due to the absence of evidence.

3.1.3 Plausibility

ALA and LA cannot be synthesised by humans. Both fatty acids are precursors to essential long-chain (≥ 20 carbon) PUFAs belonging to the ω -3 and ω -6 groups, respectively, which are synthesised through a series of elongation and desaturation reactions (Barceló-Coblijn and Murphy 2009; Alhazzaa et al. 2013).

Both ALA and LA are converted to their respective ω -3 and ω -6 long-chain metabolites by the same set of enzymes. However the biosynthesis products along the pathways are structurally distinct as are their biological roles (Anderson and Ma 2009; Choque et al. 2014). Both ω -3 and ω -6 PUFA are important structural components of cell membranes and are precursors to bioactive lipid mediators as well as being a source of metabolic energy (Uauy

et al. 2000; Innis 2007). Therefore, it is plausible that the intake of both ALA and LA can affect growth and development in children.

3.2 Applicability to Australia and New Zealand

3.2.1 Intake required for effect

Not assessed due to the absence of evidence.

3.2.2 Target population

Not assessed due to the absence of evidence.

3.2.3 Extrapolation from supplements

Not assessed due to the absence of evidence.

3.2.4 Adverse effects

Not assessed due to the absence of evidence.

4 Conclusion

Due to the lack of evidence in humans, FSANZ considers that the dietary intake of ALA and LA together being needed for normal growth and development in children (12 months of age and older but less than 18 years old) is not assessable.

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Appendix 1: Search terms

The following search terms were used in different databases to identify studies for including in the review:

MEDLINE – PubMed portal

Searched on 4th March 2015 using the following MeSH terms:

("Fatty Acids, Essential/administration and dosage"[Mesh] OR "Fatty Acids, Essential/deficiency"[Mesh] OR "Fatty Acids, Essential/therapy"[Mesh])

Limited to: Species: Human

No date limits applied

(Retrieved 1785 results)

Cochrane CENTRAL

Searched on 3rd March 2015 for:

“essential fatty acid” in title, abstract or keyword.

No limits applied.

(Retrieved 286 results)

EMBASE

Searched on 10th March 2015 for:

1. 'essential fatty acid' AND [humans]/lim (Retrieved 3149 results)
2. 'essential fatty acid' AND 'alpha linolenic acid' AND 'linoleic acid' AND [humans]/lim (Retrieved 54 results)
3. 'deficiency' AND 'alpha linolenic acid' AND 'linoleic acid' AND [humans]/lim (Retrieved 22 results)

Appendix 2: Studies excluded at full text review

	Study ID	Reason for Exclusion
1.	(Anon 1959)	Review article
2.	(Anon 1985)	Review article
3.	(Anon 1986)	Review article
4.	(Ballabriga and Martinez 1976)	Biochemical assessment of essential fatty acid deficiency (EFAD) only; no clinical changes associated with ALA and LA intervention have been reported.
5.	(Barr et al. 1981)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
6.	(Barr et al. 1981)	One of the three patients included in this study was 13 years old, the other two were adults, but no changes associated with growth or development were reported.
7.	(Berg et al. 1976)	Adult subject.
8.	(Bistran et al. 1981)	Adult subject.
9.	(Bjerve 1985)	Language translation not available (Norwegian). Cases reported likely to have been included in other English language reports in this series by the same authors.
10.	(Bjerve 1987)	Adult subject.
11.	(Bjerve et al. 1986)	Language translation not available (Norwegian). Cases reported likely to have been included in other English language reports in this series by the same authors.
12.	(Bjerve et al. 1987a)	Adult subject.
13.	(Bjerve et al. 1987b)	Adult subjects.
14.	(Bjerve et al. 1987c)	Adult subjects.
15.	(Bjerve et al. 1988)	Background diet included PUFA other than ALA and LA. The intervention is mixed with PUFA other than ALA and LA from fish oil.

	Study ID	Reason for Exclusion
16.	(Bozian and Moussavian 1982)	Letter to the journal editor commenting on another study. Does not include any new case studies.
17.	(Bozian and Piepmeyer 1976)	Letter to the journal editor commenting on another study. Does not include any new case studies.
18.	(Brown et al. 1937)	Adult subject.
19.	(Burney et al. 1979)	Infant subject.
20.	(Caldwell et al. 1972)	Infant subject.
21.	(Cederholm et al. 1994)	Adult subject.
22.	(Chase et al. 1979)	Chronically ill children subjects on a background diet containing PUFA other than ALA and LA.
23.	(Collins and Connelly 1965)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
24.	(Collins et al. 1971)	Adult subject.
25.	(Cooke et al. 1985)	Infant subjects.
26.	(Darmstadt et al. 2000)	One infant and one child subject. Baseline diet of subjects was not free of PUFA other than ALA and LA. Dietary intervention does not appear to be exclusively fatty acid.
27.	(de Meijer et al. 2009)	Letter to the editor, does not contain new case study data suitable for assessment.
28.	(de Meijer et al. 2010)	Infant subjects.
29.	(Dodge et al. 1975)	Infant subject.
30.	(Duerksen and McCurdy 2005)	Adult subjects.
31.	(Esteve-Comas and Gassull 2001)	Letter to the editor, does not contain new case study data suitable for assessment
32.	(Faintuch et al. 1976)	In Portuguese. Retrieved later as reported in English in Faintuch et al. (1977).

	Study ID	Reason for Exclusion
33.	(Faintuch et al. 1977)	Adult subjects.
34.	(Farrell et al. 1988)	Infant subjects.
35.	(Fleming et al. 1976a)	Adult subjects.
36.	(Fleming et al. 1976b)	Adult subjects.
37.	(Freund et al. 1979)	Adult subjects.
38.	(Friedman et al. 1976)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
39.	(Goodgame et al. 1978)	Did not assess any outcomes relevant to growth or development.
40.	(Gröer 1919)	Study did not include a phase where ALA or LA was reintroduced to therapy to address reported clinical changes
41.	(Gura et al. 2005)	Seriously-ill soy-allergic patient on therapeutic medications received ALA and LA intervention mixed with other PUFA from fish oil.
42.	(Hansen and Wiese 1954)	Did not assess clinical changes related to growth or development.
43.	(Hansen et al. 1958)	Infant subjects.
44.	(Hansen et al. 1963)	Infant subjects.
45.	(Heymans et al. 1982)	Background diet included ALA, LA and other PUFA. The frequency of the intervention with Intralipid® was very low (once per week for 2 months) then was followed by topical application of sunflower oil.
46.	(Hirono et al. 1977)	Did not assess growth or any aspects of development.
47.	(Hirono et al. 1977)	Infant subjects.
48.	(Holman et al. 1982a)	Seriously-ill patient lost 3m of intestine on PN with remarkably high ALA in the background diet.
49.	(Holman et al. 1982b)	Letter to the editor

	Study ID	Reason for Exclusion
50.	(Hurgoiu et al. 1986)	Infant subjects.
51.	(Igarashi et al. 1989)	Infant subject.
52.	(James and Lovelock 1958)	Review article without new case studies.
53.	(Jeejeebhoy et al. 1973)	Adult subjects.
54.	(Jeppesen et al. 1997)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
55.	(Jeppesen et al. 1998)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes
56.	(Jeppesen et al. 1999)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
57.	(Kellenberger et al. 1979)	Adult subjects.
58.	(Koletzko and Cunnane 1988)	Letter without new case studies.
59.	(Kong 1981)	Review article without new case studies.
60.	(Landon et al. 1981)	Background diet contained ALA, LA besides to other PUFA.
61.	(Le et al. 2009)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
62.	(Lee et al. 1993)	Infant subjects.
63.	(Levy et al. 1990)	This study of a child did not assess growth or development.
64.	(Martin et al. 1990)	Adult subject.
65.	(Mascioli et al. 1979)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
66.	(Mascioli et al. 1996)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.

	Study ID	Reason for Exclusion
67.	(McCarthy et al. 1978)	This study of a child did not assess growth or development.
68.	(Meldrum et al. 1976)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
69.	(Mischler et al. 1986)	Did not report clinical changes in subjects. Also, not all subjects are children.
70.	(O'Neill et al. 1977)	Did not assess any outcomes related to growth or development.
71.	(Paassilta et al. 2014)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
72.	(Panteliadis 1977)	Infant subjects.
73.	(Parsons et al. 1988)	Did not report on clinical changes in participants.
74.	(Paulsrud et al. 1972)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
75.	(Peck et al. 1996)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
76.	(Petrovic et al. 1964)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
77.	(Pettei et al. 1991)	Study in infants.
78.	(Piper et al. 1986)	Study in adults.
79.	(Postuma et al. 1978)	Study in infants.
80.	(Press et al. 1974)	Study in adults.
81.	(Presser et al. 1983)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
82.	(Richardson and Sgoutas 1975)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
83.	(Roongpisuthipong et al. 2012)	Study in adults.

	Study ID	Reason for Exclusion
84.	(Ruiz et al. 2001)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
85.	(Sacks et al. 1994)	Study in adults.
86.	(Siguel et al. 1986)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
87.	(Siguel et al. 1987)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
88.	(Socha et al. 1998)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
89.	(Socha et al. 2005)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
90.	(Stein et al. 1980)	Study in adults.
91.	(Stein et al. 1983)	Study in adults.
92.	(Steinkamp et al. 2000)	Other PUFA were included in the intervention besides to ALA and LA.
93.	(Strandvik et al. 1989)	Did not report clinical changes related to growth and development in participants.
94.	(Tanphaichitr et al. 1979)	Study in adults.
95.	(van Egmond et al. 1996)	Study in infants.
96.	(von Chwalibogowski 1937)	Study did not include a phase where ALA and LA were reintroduced to therapy to address reported clinical changes.
97.	(Warwick et al. 1959)	Study in infant.
98.	(Wene et al. 1975)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.
99.	(Yamanaka et al. 1980)	Review article without new case studies.
100.	(Yoshimoto et al. 1999)	Biochemical assessment of EFAD only; no clinical changes associated with ALA and LA intervention have been reported.

Appendix 3: GRADE summary of findings tables

Question: *Is dietary intake of α -linolenic and linoleic acids (ALA and LA) together needed for normal growth and development in children (aged ≥ 1 to < 18 years)?*

Quality assessment of body of evidence							Participant numbers	Mean effect size	Quality (degree of certainty)
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Considerations			
All symptoms potentially related to normal growth and development in children									
0	n/a	n/a	n/a	n/a	n/a	None	0	Not estimated	Not assessable