



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

**Systematic review of the evidence for a
relationship between docosahexaenoic acid
(DHA) and maintenance of normal brain
function and normal vision**

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Date: October 2015

Executive Summary

Is dietary intake of docosahexaenoic acid (DHA) required to maintain normal brain function?

Food health relationship	Dietary intake of DHA is required to maintain normal brain function
Proposed degree of certainty (GRADE rating)	Non-assessable

Component	Notes
<i>Body of evidence</i>	No suitable human case reports, case series or clinical trials examining the effects of deficiency of dietary DHA were identified and, therefore, none were included in this systematic review.
<i>Consistency</i>	There was no body of evidence to assess for consistency.
<i>Causality</i>	There was no body of evidence to assess from which to draw a conclusion about causality.
<i>Plausibility</i>	It is plausible that dietary deficiency of the lipid could influence normal brain function, as DHA is a major fatty acid component of the human brain. However DHA is formed in the body from polyunsaturated fatty acids, most notably alpha-linolenic acid.
<i>Generalisability</i>	No suitable studies could be identified in humans. Generalisability to food or property of food for consumption by healthy individuals is not applicable.

Is dietary intake of docosahexaenoic acid (DHA) required to maintain normal vision?

Food health relationship	Dietary intake of DHA is required to maintain normal vision
Proposed degree of certainty (GRADE rating)	Non-assessable

Component	Notes
<i>Body of evidence</i>	No suitable human case reports, case series or clinical trials examining the effects of deficiency of dietary DHA were identified and, therefore, none were included in this systematic review.
<i>Consistency</i>	There was no body of evidence to assess for consistency.
<i>Causality</i>	There was no body of evidence to assess from which to draw a conclusion about causality.
<i>Plausibility</i>	It is plausible that dietary deficiency of the lipid could influence normal vision, as DHA is a major fatty acid component of the human retina. However DHA is formed in the body from polyunsaturated fatty acids, most notably alpha-linolenic acid.
<i>Generalisability</i>	No suitable studies could be identified in humans. Generalisability to food or property of food for consumption by healthy individuals is not applicable.

FSANZ has conducted a systematic review on dietary deficiency of DHA and the maintenance of normal brain and vision functions. In doing this review, FSANZ has followed the requirements of the *Application Handbook* and of Schedule 6 of Standard 1.2.7 – Nutrition, Health and Related Claims, for the required elements of a systematic review.

FSANZ identified five case studies in which seriously ill patients received DHA. However, none of these studies assessed any aspect of brain or vision functions after the intervention.

Due to the lack of suitable human studies of DHA and maintenance of normal brain and vision functions, FSANZ regards the two relationships that are the subject of this review as being 'non-assessable'.

Contents

- 1 Introduction 1
 - 1.1 Food or the property of food 1
 - 1.2 Health effect 2
 - 1.3 Proposed relationships 2
- 2 Evaluation of evidence 3
 - 2.1 Methods 3
 - 2.1.1 Search strategy 3
 - 2.1.2 Inclusion and exclusion criteria 3
 - 2.1.3 Study selection, data extraction and quality assessment 4
 - 2.1.4 Statistical analyses 5
 - 2.1.5 Subgroup analyses 5
 - 2.2 Results 5
 - 2.2.1 Search results 5
 - 2.2.2 Included studies 5
 - 2.2.3 Quality assessment of studies 5
 - 2.3 Summary of evidence 6
 - 2.3.1 DHA and normal brain function 6
 - 2.3.2 DHA and normal vision 7
- 3 Weight of evidence 7
 - 3.1 Assessment of body of evidence 7
 - 3.1.1 Consistency of relationship 7
 - 3.1.2 Causality 7
 - 3.1.3 Plausibility 7
 - 3.2 Applicability to Australia and New Zealand 8
 - 3.2.1 Intake required for effect 8
 - 3.2.2 Target population 8
 - 3.2.3 Extrapolation from supplements 8
 - 3.2.4 Adverse effects 8
- 4 Conclusion 8
- 5 References 8
- Appendix 1: Search terms 17
- Appendix 2: Studies excluded at full text review 18
- Appendix 3: GRADE summary of findings tables 25

1 Introduction

In 2012, the European Union (EU) authorised (Commission Regulation (EU) No. 432/2012) two health claims about the relationship between docosahexaenoic acid (DHA) and its contribution to the maintenance of normal brain function and normal vision. FSANZ notes that the condition associated with both claims was that “the claim may be used only for food which contains at least 40 mg of DHA per 100 g and per 100 kcal. In order to bear the claim, information shall be given to the consumer that the beneficial effect is obtained with a daily intake of 250 mg of DHA”.

In examining the evidence to support both these claims, the European Food Safety Authority (EFSA) noted that DHA is a major structural lipid in the human brain and retina (EFSA Panel on Dietetic Products 2010). They also cited the United States Institute of Medicine’s (IoM) 2005 review of dietary requirements for lipids (IoM 2005). The IoM review concluded that alpha-linolenic acid (ALA), i.e. the precursor fatty acid for omega-3 long-chain (\geq C20) polyunsaturated fatty acids (n-3 LC-PUFAs) such as DHA, is an essential nutrient. While recommending a dietary intake of ALA, the IoM did not recommend that the dietary intake of DHA is essential.

FSANZ notes that neither EFSA nor IoM carried out systematic reviews of the literature to examine the relationships between consumption of DHA and the maintenance of normal brain function and vision. FSANZ also noted that EFSA made its recommendations based on the IoM report (IoM 2005) by considering the adverse clinical symptoms of ALA deficiency as the evidence for DHA, the end-product of ALA endogenous conversion, in maintaining normal both brain function and vision. EFSA has also considered other evidence for the structural and biochemical role of DHA in the human brain and neural tissue in the eye to support the claims. However, EFSA did not consider the evidence for the relationship of dietary intake of DHA and the contribution to the maintenance of normal brain function and normal vision (EFSA Panel on Dietetic Products 2010).

FSANZ is considering whether a relationship between DHA and the maintenance of normal brain function and normal vision can be incorporated into Schedule 3 of Standard 1.2.7 – Nutrition, Health and Related Claims. FSANZ considers that ‘contributes to the maintenance’ is part of the wording specifications for the EU claim. Therefore, the relationships to be investigated by FSANZ are that dietary intake of DHA is required to maintain normal brain and that dietary intake of DHA is required to maintain normal vision. The purpose of this paper is to systematically review the evidence for these relationships.

1.1 Food or the property of food

DHA is a well-characterised n-3 LC-PUFA containing 22 carbon atoms and six *cis* unsaturated bonds (i.e. double bonds), the first of which is at the third carbon atom counting from the omega end of the carbon chain. DHA is abundant in marine oils and oily marine fish (e.g. mackerel, tuna, salmon, sardines and herring). DHA rarely exists as a free fatty acid in food and usually occurs in the triglyceride form, with lesser amounts present in a phospholipid form (Haraldsson and Hjaltason 2001; Strigley and Rader 2014). Humans can biosynthesise only small amounts of n-3 LC-PUFA from precursors, such as ALA, which is available from vegetable oils (Goyens et al. 2006; Brenna et al. 2009). Food sources rich in DHA are few, especially since terrestrial edible plants cannot make this fatty acid. Most human populations receive their dietary DHA directly from the seafood they consume or through maternal nutrition (i.e. breastfeeding) for infants. Natural accumulation of DHA occurs throughout the marine food web, starting mainly from algae and lower fungi that are capable of synthesising DHA. Small crustaceans and forage fish feed on algae and lower

fungi to obtain nutrients including DHA that accumulate in larger amounts in the tissues of predatory fish (Bell and Tocher 2009; Gladyshev et al. 2013). In line with that fact, the main food source of DHA for Australians and New Zealanders is seafood and marine oils (Meyer et al. 2003; NHMRC 2005; University of Otago and Ministry of Health 2011; Australia Bureau of Statistics 2014).

After extraction with an organic solvent and conversion to the corresponding methyl ester, DHA content in food and blood serum or plasma is mainly measured by gas chromatography (GC) with flame ionization detection (GC-FID) and, when necessary, with mass spectrometric detection (MS) (Christie 1998; AOAC 2000).

For the purpose of these food-health relationships, only DHA as a fatty acid in triglyceride, phospholipid or other lipid forms is considered. Oil mixtures rich in DHA such as fish oil and other n-3 LC-PUFA such as eicosapentaenoic acid (EPA) or docosapentaenoic acid (DPA) are not the subject of this of this systematic review.

1.2 Health effect

The abovementioned EU claims are non-specific in describing what aspects of normal brain or vision functions the claims relate to. Therefore, FSANZ used a broad definition of the health effects in the systematic review.

Brain function could include any aspect of cognitive, behavioural, psychological or neural brain functions. Cognitive, behavioural and psychological functions are assessed mainly by psychometric testing, such as computerised batteries of tests (tasks and cognitive skills), the Bayley Scales and normative scores like intelligence quotient (IQ) amongst few other methods (Ryan and Nelson 2008; Politi et al. 2008; Kennedy et al. 2009; Sun et al. 2015). Neural brain functions are frequently assessed, amongst many other valid techniques, by biochemical, molecular and imaging techniques as well as neurodegenerative and neuromotor activity assessments such as Alzheimer's Disease Assessment Scale (Martinez and Vazquez 1998; Wurtman et al. 2009; Quinn et al. 2010; Bauer et al. 2014). These methods of assessment have been widely used, standardised and referenced in scientific articles related to brain functions.

The definition of vision could include visual acuity, macular health and retinal neural activity. Visual acuity is usually assessed by standardised measurements employing numerical or graphical charts, such as Snellen chart, electrophysiology and electroretinography utilising contact lens electrodes (Uauy et al. 1990; Birch et al. 2010; Berson et al. 2012). Retinal activity, macular degeneration, maculopathy and optical density of macular pigment are also assessed frequently by several standardised methods such as fundus and photographic grading, retinal pigmentation and drusen diagnosis (Chong et al. 2008; Kishan et al. 2011; Stough et al. 2012). These standard methods can assess and quantify vision functions effectively and have been widely used and cited in scientific literature related to vision function.

1.3 Proposed relationships

The food-health relationships being assessed in this report are:

- Dietary intake of DHA is required to maintain normal brain function.
- Dietary intake of DHA is required to maintain normal vision.

2 Evaluation of evidence

The relationship investigated by FSANZ was that dietary intake of DHA is required to maintain normal brain function and/or normal vision, rather than increased DHA intake enhancing these functions. Therefore FSANZ has examined the evidence for dietary deficiency of DHA.

FSANZ could not identify an existing systematic review of DHA-deficient diets in humans and development of clinical symptoms related to brain function or vision that were reversed by the administration of DHA. Therefore, a new systematic review was undertaken.

2.1 Methods

2.1.1 Search strategy

Owing to the scarcity of data and because some relevant articles refer to ALA or LA, a broad electronic database 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 DHA. Therefore, no specific outcome measures were included in the search.

Searches were conducted in EMBASE, PubMed and Cochrane CENTRAL between the 3rd and the 10th of March 2015. Detailed search strategies are presented in Appendix 1. In EMBASE and PubMed, Medical Subject Headings (MeSH) terms were used to refine the scope of the search results. PubMed results were limited to studies in humans. No date limits were applied to any searches. Additional references were also identified by hand-searching the reference lists of studies assessed at the full-text stage of screening.

The Australia New Zealand and WHO Clinical Trials Registries were searched on 28 July 2015 for 'essential fatty acid'. Only one study (ACTRN12610000616077, from 2010, retrospectively registered) was identified as being potentially relevant to this review. A paper that appears to be the result of that study (Bauer et al. 2014) was located. However, the paper was identified as a review article. Other identified registered trials did not include DHA as the intervention, did not examine the effects of deficiency, or did not examine the maintenance of normal functions.

To check the validity of the literature search strategy, FSANZ examined the reference lists cited by the EFSA opinion (EFSA Panel on Dietetic Products 2010), the National Health and Medical Research Council and New Zealand Ministry of Health (NHMRC and NZ MoH, 2006) and the US Institute of Medicine (IoM 2005). All relevant studies cited in these reports were contained in the literature retrieved using the search strategy shown in Appendix 1. Therefore FSANZ believes that no relevant literature has been missed.

2.1.2 Inclusion and exclusion criteria

Studies to be included were not limited to a particular study design, as relevant information may have been found in case reports, case series, randomised trials or some other designs. Study subjects and participants could be adults or children 12 months of age and older. No exclusion criteria were set based on the health of subjects or participants. The eligibility criteria are summarised in Table 1. DHA intervention could be given in various ways, such as an oil emulsion added to parenteral or enteral feeding, or a specific fatty acid ester. To be included, studies must have included both a lipid-free (or negligible lipid) phase and a phase where DHA was added to the baseline diet. Studies using mixtures of fatty acids that included DHA as the intervention and compared with a control treatment receiving the same

mixture of fatty acid but lacking DHA were included as the difference in the assessed effect on brain or vision functions was likely attributed to the intervention with DHA. Therefore studies in which symptoms of lipid deficiency were reported but no lipid was administered to treat these symptoms were excluded.

To be included, studies must have provided information on clinical changes in participants. Studies where the only reported changes were in biochemical parameters, such as plasma levels of fatty acids and/or DHA, were excluded. While many authors regard the appearance in plasma of the 20:3 n-9 (mead acid) or an elevated ratio of that fatty acid to that of 20:4 n-6 (arachidonic acid), as being diagnostic of fatty acid deficiency, there does not appear to be a consensus on the diagnostic value of this ratio and, therefore, only clinical criteria were used as the outcome. However, where included studies reported one or both of these parameters, this information was recorded. No minimum study duration was set.

Table 1 PICOTS criteria for study selection

Population	Participants 12 months of age and older maintained on DHA-free or extremely low DHA diets or nutrition support regimens with participants experiencing clinical signs or symptoms before intervention.
Intervention	DHA source added to nutrition support, including oils or as pure fatty acid esters.
Comparator	For case studies, comparator is the same individual before DHA intervention was initiated. For trials, comparator is participants who either continued on a DHA-free diet or received other fatty acid mixtures lacking DHA.
Outcome	All reported clinical and behavioural signs or symptoms related to brain and vision functions.
Time	No limits.
Study design	Randomised controlled trials, clinical trials, case series or case reports.

Exclusion criteria

The following exclusion criteria were established:

- Studies where the outcome was changes in plasma or serum lipid profile, without accompanying clinical signs or symptoms
- Patients who were given multiple concurrent dietary interventions, including EPA or other fatty acids
- Patients who did not have clinical signs or symptoms of deficiency before DHA intervention was initiated.
- Diets that contained substantial lipid or DHA intake before the intervention, for example from concurrent food consumption
- Studies involving enhanced intake, i.e. above the normal dietary intakes in healthy populations.

2.1.3 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 removal of duplicates, records were screened on title and abstract. Candidate 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. 2011).

2.1.4 Statistical analyses

Neither meta-analysis nor another type of statistical analysis was undertaken as there were no included studies with data to extract and compare.

2.1.5 Subgroup analyses

No sub-group analysis has been carried out due to the lack of studies and populations to compare.

2.2 Results

2.2.1 Search results

The screening of articles retrieved from the search strategies is detailed in Figure 1. Studies excluded after full text examination are listed in Appendix 2. No studies were included.

2.2.2 Included studies

There were 98 studies screened on full text but they were all excluded for not meeting one or more of the PICOTS criteria. Of the 98 studies screened on full text, there were five studies (Bjerve et al. 1987a; Bjerve et al. 1988; Bjerve 1989; Bjerve et al. 1989; Gura et al. 2005) administering DHA as an intervention but within a mixture of other fatty acids, without an appropriate comparator and without assessing any aspect of brain or vision function. Therefore, no studies meeting the PICOTS criteria were found in this systematic review to be included for further assessment.

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 in this review.

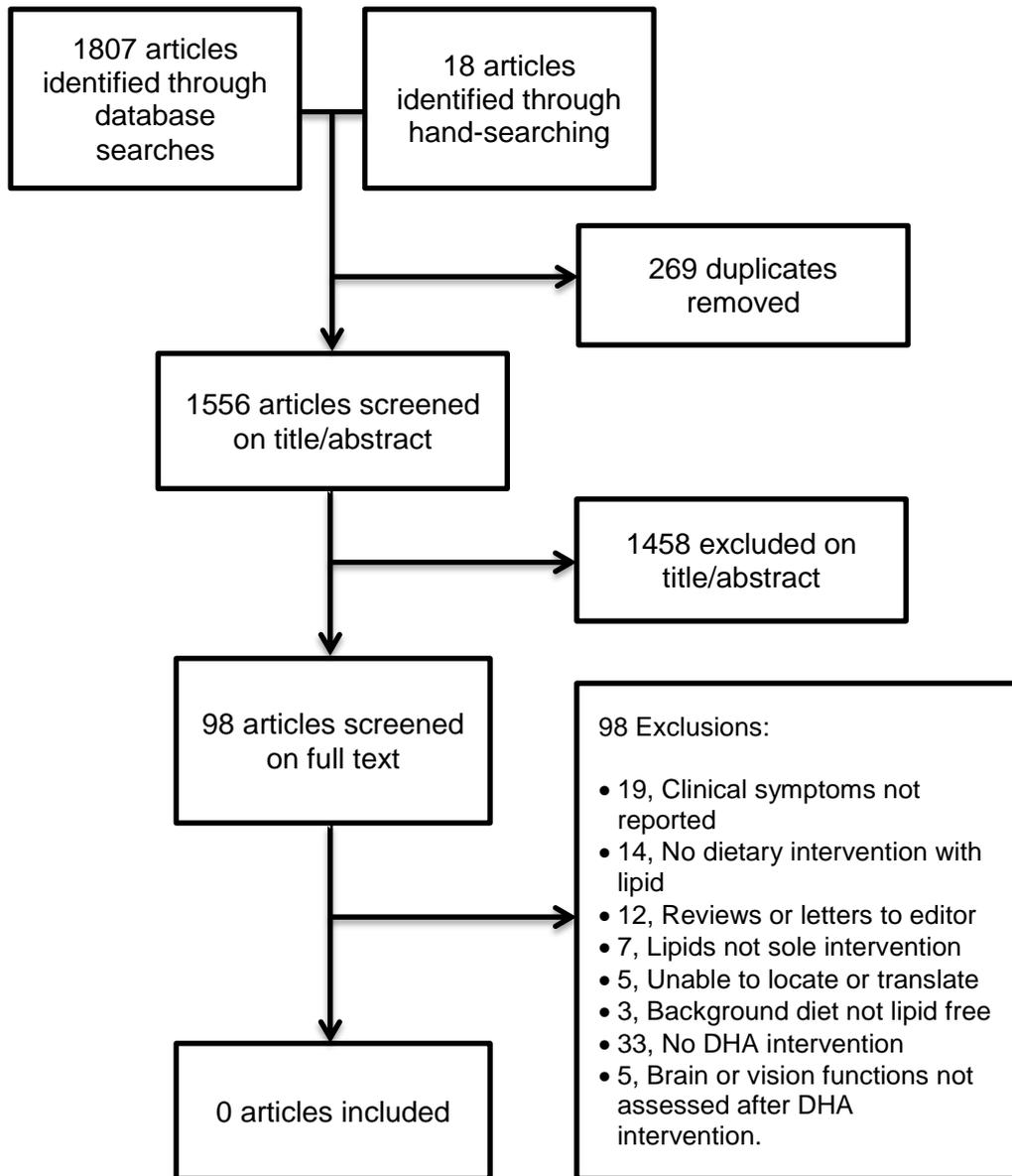


Figure 1. PRISMA diagram of study identification process

2.3 Summary of evidence

2.3.1 DHA and normal brain function

There were no studies identified that used DHA as the intervention followed by the assessment of any aspect of brain functions following the intervention. Therefore, there is no evidence to be assessed.

2.3.2 DHA and normal vision

There were no studies identified that used DHA as the intervention followed by the assessment of change in vision following the intervention. Therefore, there is no evidence to be assessed.

3 Weight of evidence

This systematic review aimed to identify all available human studies examining the contribution of DHA, as food or a property of food, in the maintenance of normal brain function and normal vision and whether clinical symptoms of compromised normal brain function and normal vision subsequently improved or resolved with the consumption of DHA.

To ensure that all studies might be captured, a broad search strategy was designed. Of the 98 articles screened on full text, no studies were identified that met the inclusion criteria. Some case reports of seriously ill patients used Intralipid® (emulsion of soy bean oil, egg phospholipids and glycerine) parenteral intervention that did not contain DHA and some other case reports of other seriously ill patients used DHA as the intervention but did not assess brain or vision functions. Therefore, no evidence derived from human studies was identified that could be used to establish a relationship between dietary DHA and maintenance of normal brain function or normal vision.

For a food-health relationship to be substantiated there has to be a consistent effect across high quality studies. No high quality studies, or, indeed, low quality studies, were identified in this review. Thus, as there is no available evidence, FSANZ concludes the relationships between DHA and normal brain function or between DHA and normal vision are both non-assessable.

FSANZ notes that there are some studies in infants, who are under the age of 12 months as defined in Standard 2.9.1 of the *Australia New Zealand Food Standards Code*, that examined brain and vision functions following feeding of DHA-rich formula. However, as health claims are not allowed on infant formula product within the current regulatory framework, these studies were not within the scope of this systematic review and their outcomes cannot be extrapolated to adults. Furthermore, FSANZ is also aware that there are a considerable number of human studies examining the effects of *enhanced* intake of n-3 LC-PUFA on selected aspects of brain or vision functions, or in the treatment of neurological or psychiatric conditions, rather than the *maintenance* of normal brain or normal vision functions.

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

DHA serves as a key component in neurotransmission and cell membrane structure in the brain and retina (Salem, Jr. et al. 2001; Rapoport et al. 2011). Therefore it is plausible that intake of DHA could affect the function of these organs as well. However, DHA can be formed in the body from its precursors which are other n-3 polyunsaturated fatty acids such as ALA, which is found in terrestrial vegetable oils. Other n-3 LC-PUFA such as EPA or DPA

can also be endogenously converted into DHA (Bjerve 1989; Brenna et al. 2009). The properties of DHA have been shown to include effects on cerebral and retinal neuronal development and plasticity, receptor-mediated signalling, changes in membrane fluidity, the formation of second messengers, and/or enhancement of the production of anti-inflammatory lipid mediators due to the availability of DHA as a substrate (Salem, Jr. et al. 2001; SanGiovanni and Chew 2005; Bazan 2005).

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, FSANZ considers that relationships between dietary DHA intake and the maintenance of normal brain function or dietary DHA intake and the maintenance of normal vision, are non-assessable.

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Appendix 1: Search terms

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

Medline – PubMed portal

Searched 4 March 2015 using the following MeSH terms:

((("fatty acids, essential/administration and dosage"[MeSH Terms])) OR "fatty acids, essential/deficiency"[MeSH Terms]) OR "fatty acids, essential/therapy"[MeSH Terms]

Limited to: Species: Human

No date limits applied.

(Retrieved 1785 results)

Cochrane Library (Central)

Searched 3 March 2015 for:

"Essential fatty acid" in Title, Abstract, Keywords and "docosahexaenoic acid" in Title, Abstract, Keywords and "deficiency" in Title, Abstract, Keywords , No limits applied.

(Retrieved 14 results)

Embase®

Searched 10 March 2015 for:

1. 'essential fatty acid' AND [humans]/lim (Retrieved 3152 results)
2. 'essential fatty acid' AND 'docosahexanoic acid' AND [humans]/lim (Retrieved 18 results)
3. 'essential fatty acid' AND 'docosahexanoic acid' AND deficiency AND [humans]/lim (Retrieved 8 results)

Appendix 2: Studies excluded at full text review

	Study ID	Reason for Exclusion
1.	(Anon 1959)	Review article without new studies.
2.	(Anon 1985)	Review article without new studies.
3.	(Anon 1986)	Review article without new studies.
4.	(Ballabriga and Martinez 1976)	Biochemical assessment of EFAD only, which is not specific to DHA. No reported clinical changes associated with EFAD
5.	(Barr et al. 1981)	Biochemical assessment of EFAD only, which is not specific to DHA. No clinical changes associated with these biochemical changes were reported.
6.	(Berg et al. 1976)	Cronkhite-Canada Syndrome patient. PN fatty acid intervention but not clear if it contained DHA or not.
7.	(Bistran et al. 1981)	Although this study described clinical changes the authors attributed to EFAD, it did not include a phase where lipid was reintroduced to enteral or parenteral therapy to address these reported clinical changes. Treatment of the patient included topical application of oils.
8.	(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.
9.	(Bjerve 1989)	Brain-damaged bedridden patient received lipid containing DHA with other EFA as oil. Brain or vision functions were not assessed.
10.	(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.
11.	(Bjerve et al. 1987b)	Bedridden tube-fed patient. Enternal fatty acid intervention did not include DHA.
12.	(Bjerve et al. 1987a)	Bedridden brain-damaged patients received lipid containing DHA with other EFA as oil through gastric tube. Brain or vision functions were not assessed.
13.	(Bjerve et al. 1987c)	Bedridden and tube-fed patient. Enternal lipid intervention without DHA.

	Study ID	Reason for Exclusion
14.	(Bjerve et al. 1988)	Tube-fed patient with genetic disorder received DHA with other EFA as intervention. However, brain or vision functions were not assessed.
15.	(Bjerve et al. 1989)	Bedridden brain-damaged patients received lipid containing DHA with other EFA as oil through gastric tube. Brain or vision functions were not assessed.
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 WR et al. 1937)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes
19.	(Burney et al. 1979)	Seriously ill infant (3 weeks old) patient. Not clear if the PN dietary intervention included DHA. Brain and vision functions were not assessed.
20.	(Caldwell et al. 1972)	Seriously ill infant (6 months old) patient. Brain and vision functions not assessed. Intralipid intervention did not include DHA.
21.	(Cederholm et al. 1994)	Participants were not on a lipid-free background diet, although were malnourished due to disease. The only clinical changes assessed were for delayed cutaneous hypersensitivity
22.	(Chase et al. 1979)	Participants were not on a lipid-free background diet
23.	(Collins and Connelly 1965)	Biochemical assessment of EFAD only with no clinical data. Not relevant to DHA.
24.	(Collins et al. 1971)	Chronic patient. Intralipid intervention did not include DHA.
25.	(Darmstadt et al. 2000)	Chronically-ill patients with signs of EFAD, not relevant to DHA. Dietary intervention does not appear to be exclusively lipid. No brain or vision functions were assessed.
26.	(de Meijer et al. 2009)	Letter to the editor, does not contain new case study data suitable for assessment.
27.	(de Meijer et al. 2010)	Study did not include a phase where participants received a lipid free diet. All patients were either maintained on PN with fish oil added or switched from PN with soy oil.
28.	(Dodge et al. 1975)	Chronically-ill infant (3 days old). Parenteral intralipid intervention did not include DHA and no assessment for brain or vision reported.
29.	(Duerksen and McCurdy 2005)	Severely malnourished anorexic patient. Intralipid intervention did not include DHA.

	Study ID	Reason for Exclusion
30.	(Esteve-Comas and Gassull 2001)	Letter to the editor, does not contain new case study data suitable for assessment
31.	(Faintuch et al. 1976)	The same cases as later reported in Faintuch et al. 1977
32.	(Faintuch et al. 1977)	Malnourished, GI surgery patient. Dietary fatty acid intervention but did not include DHA.
33.	(Fleming et al. 1976a)	Chronically ill patients. Lipid dietary intervention did not include DHA. No assessment for brain or vision functions.
34.	(Fleming et al. 1976b)	Lipid dietary intervention did not include DHA. No assessment for brain or vision functions.
35.	(Freund et al. 1979)	Chronic patients. Intralipid intervention with PN fatty acid intervention but did not include DHA.
36.	(Friedman et al. 1976)	Biochemical assessment of EFAD only which is not specific to DHA. No reported clinical changes associated with EFAD. Participants were not given lipid therapy (blood transfusions were provided).
37.	(Goodgame et al. 1978)	Cancer patient with signs of essential fatty acid deficiency. Intralipid intervention with PN fatty acid intervention but did not include DHA.
38.	(Gröer 1919)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes
39.	(Gura et al. 2005)	Chronically-ill patient receiving fish oil capsules containing DHA and other EFA. Brain or vision functions were not assessed.
40.	(Hansen and Wiese 1954)	Study examined serum plasma only and did not assess clinical changes or effects of supplying additional lipids
41.	(Hansen et al. 1958)	Infants (up to 12 months old). Dietary fatty acid intervention but did not include DHA.
42.	(Hansen et al. 1963)	Full term infants (up to 12 months old). Dietary fatty acid intervention but did not include DHA.
43.	(Heymans et al. 1982)	Chronically-ill patient receiving intralipid intervention with PN fatty acid intervention but did not include DHA. Brain and vision functions were not assessed.
44.	(Hirono et al. 1977)	Seriously ill infant (2-5 months old) patients. Intralipid intervention did not include DHA. Brain and vision functions not assessed.
45.	(Holman et al. 1982)	Seriously-ill patient on PN intervention but did not include DHA.

	Study ID	Reason for Exclusion
46.	(Hurgoiu et al. 1986)	Premature infants. Language translation not available (Romanian).
47.	(Igarashi et al. 1989)	Chronically-ill patients (1-month old infant and a 12-year old child) on PN that did not clearly include DHA. Brain or vision functions were not assessed.
48.	(James and Lovelock 1958)	Review article without new studies.
49.	(Jeejeebhoy et al. 1973)	Chronically-ill patient. Intralipid intervention did not include DHA.
50.	(Jeppesen et al. 1997)	Study did not include a phase where lipid or DHA were reintroduced to therapy to address reported clinical changes
51.	(Jeppesen et al. 1998)	Study did not include a phase where lipid or DHA were reintroduced to therapy to address reported clinical changes
52.	(Jeppesen et al. 1999)	Biochemical assessment of EFAD only. Not specific to DHA and no reported clinical changes.
53.	(Kellenberger et al. 1979)	Chronically-ill patient on PN intralipid intervention without DHA. Brain and vision functions not assessed.
54.	(Koletzko and Cunnane 1988)	Letter without new studies.
55.	(Kong 1981)	Review article without new studies.
56.	(Landon et al. 1981)	Background diet not lipid free. No DHA intervention.
57.	(Le et al. 2009)	Biochemical assessment of essential fatty acid deficiency (EFAD) only; no reported clinical changes associated with EFAD
58.	(Lee et al. 1993)	Intralipid intervention with PN fatty acid intervention but did not include DHA.
59.	(Levy et al. 1990)	Seriously-ill patient on intralipid intervention without DHA. Brain and vision functions not assessed.
60.	(Martin et al. 1990)	Case study that did not include DHA intervention or assessment for brain or vision functions.
61.	(Mascioli et al. 1979)	Biochemical assessment of EFAD only which is not specific to DHA. No clinical changes reported.

	Study ID	Reason for Exclusion
62.	(Mascioli et al. 1996)	Biochemical assessment of EFAD only which is not specific to DHA. No clinical changes reported.
63.	(McCarthy et al. 1978)	Chronically-ill patient on PN intralipid intervention without DHA. Brain and vision functions not assessed.
64.	(Meldrum et al. 1976)	Biochemical assessment of essential fatty acid deficiency (EFAD) only; no reported clinical changes associated with EFAD
65.	(Meng 1983)	Review article without new studies
66.	(Mischler et al. 1986)	No DHA intervention. Did not report on clinical changes in participants and did not assess brain or vision functions.
67.	(O'Neill JA Jr et al. 1977)	Chronically-ill patients after surgeries. Mixture of intralipid intervention and PN fatty acid intervention but did not include DHA.
68.	(Paassilta et al. 2014)	Study did not include a phase where lipid was reintroduced to therapy to assess reported clinical changes
69.	(Panteliadis 1977)	Did not report clinical changes, brain or vision functions assessment in participants
70.	(Parsons et al. 1988)	Did not report clinical changes, brain or vision functions assessment in participants
71.	(Paulsrud et al. 1972)	Biochemical assessment of EFAD only which is not specific to DHA. No reported clinical changes associated with EFAD
72.	(Peck et al. 1996)	Biochemical assessment of EFAD only which is not specific to DHA. No reported clinical changes associated with EFAD
73.	(Petrovic et al. 1964)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes
74.	(Pettei et al. 1991)	Seriously-ill infant (1.5-2 months old) patients on intralipid intervention without DHA. Brain and vision functions not assessed.
75.	(Piper et al. 1986)	Dietary lipid intervention did not include DHA. Vision function was not assessed.
76.	(Postuma et al. 1978)	Seriously-ill preterm infant (2-8 days) patients on intralipid intervention without DHA. Brain and vision functions were not assessed.
77.	(Press et al. 1974)	Seriously-ill patient on intralipid intervention without DHA. Brain and vision functions not assessed.
78.	(Presser et al. 1983)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes

	Study ID	Reason for Exclusion
79.	(Richardson and Sgoutas 1975)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes
80.	(Riella et al. 1975)	Seriously-ill patient on intralipid PN intervention without DHA. Brain and vision functions not assessed.
81.	(Roongpisuthipong et al. 2012)	Critically-ill patient on intralipid PN intervention without DHA. Brain and vision functions not assessed.
82.	(Ruiz et al. 2001)	Biochemical assessment of EFAD only which is not specific to DHA. No reported clinical changes associated with EFAD
83.	(Sacks et al. 1994)	Seriously-ill patient on intralipid PN intervention without DHA. Brain and vision functions not assessed.
84.	(Siguel et al. 1986)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes. Biochemical assessment of EFAD only, which is not specific to DHA. No reported clinical changes associated with EFAD
85.	(Siguel et al. 1987)	No dietary intervention from fat free diet to one containing added lipids.
86.	(Socha et al. 1998)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes. Biochemical assessment of EFAD only, which is not specific to DHA. No reported clinical changes associated with EFAD
87.	(Socha et al. 2005)	Biochemical assessment of essential fatty acid deficiency (EFAD) only; no dietary intervention with additional lipids.
88.	(Stein et al. 1983)	Seriously-ill patient on intralipid PN intervention without DHA.
89.	(Stein et al. 1980)	PN intervention did not include DHA. Did not report on clinical changes in participants.
90.	(Steinkamp et al. 2000)	Chronically-ill patients with lipid intervention not containing DHA.
91.	(Strandvik et al. 1989)	Did not report on clinical changes in participants
92.	(Tanphaichitr et al. 1979)	Study did not include a phase where DHA alone was reintroduced to therapy to address reported clinical changes. Therapy to treat deficiency was enteral feeds (undefined) or normal diet.
93.	(van Egmond et al. 1996)	Chronically-ill infants and early children (1.5 to 15 months old). Background diet was not lipid free; study compared pre-digested formula with two different LA levels.
94.	(von Chwalibogowski 1937)	Study did not include a phase where lipid was reintroduced to therapy to address reported clinical changes

	Study ID	Reason for Exclusion
95.	(Warwick et al. 1959)	Seriously-ill patient on lipid intervention without DHA.
96.	(Wene et al. 1975)	Biochemical assessment of EFAD only, which is not specific to DHA. No reported clinical changes associated with EFAD
97.	(Yamanaka et al. 1981)	Review article without new case studies
98.	(Yoshimoto et al. 1999)	Biochemical assessment of EFAD only, which is not specific to DHA. No reported clinical changes associated with EFAD

EFAD: essential fatty acid deficiency. PN: parenteral nutrition.

Appendix 3: GRADE summary of findings tables

Question: *Is dietary intake of docosahexaenoic acid (DHA) required to maintain normal brain and vision function?*

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 brain function									
0	n/a	n/a	n/a	n/a	n/a		0	Not estimated	Non-assessable
All symptoms potentially related to normal vision									
0	n/a	n/a	n/a	n/a	n/a		0	Not estimated	Non-assessable