4.1b(i) Composition of Enteral Nutrition: Fish Oils, Borage Oils and Antioxidants* April 2017

2015 Recommendation: *Based on 3 level 1 studies and 5 level 2 studies, the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) should be considered.*

2015 Discussion: With the addition of 1 new study (Kagan 2015), the committee acknowledged that the lack of a treatment effect of enteral fish oils, borage oils and antioxidants remained. The sparse data on ventilator associated pneumonia i.e. 3 studies showing no effect, was noted. There were concerns about the adequacy of the control group in several studies (i.e. high fat formula, additional protein). Since the delivery of fish oil or fish oil/borage oil/antioxidant components as a bolus could have diminished the treatment effect, a sensitivity analysis with and without the Rice 2011 was done. A significant effect on 28 day mortality was only seen when this study was excluded. The committee agreed that the signals from the Grau-Carmona study, the first large, multicenter trial that used a 'usual care' control solution and had results were negative results still had to be considered and it was agreed to continue with a recommendation for 'should be considered'.

2013 Recommendation: *Based on 2 level 1 studies and 5 level 2 studies, the use of an enteral formula with fish oils, borage oils and antioxidants in patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) should be considered.*

Discussion 2013: The committee noted that with the addition of 3 new studies (Rice 2011, Grau-Carmona 2011, and Thiella 2011) and the update of an earlier study (Elamin 2012), the overall treatment effect on mortality decreased. There were concerns about the adequacy of the control group in the large multicentre study Rice 2011 in which the placebo solution contained 20 extra grams of protein. In addition the fish oil/borage oil/antioxidant components were administered as a bolus, which may have diminished the treatment effect. Hence a sensitivity analysis with and without the Rice 2011 study was conducted. A significant effect on 28 day mortality was only seen when the Rice study was excluded. It was further noted that the Grau-Carmona study was the first large, multicenter trial that used a 'usual care' control solution and the results were negative. After much deliberation, the committee downgraded the recommendation to 'should be considered' because of the aforementioned uncertainties.

Semi Quantitative Scoring

Values	Definition	2009 Score	2013 Score	2015 Score (0,1,2,3)
Effect size	Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size	1	1	1
Confidence interval	95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval	1	1	1
Validity	Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised	2	2	2
Homogeneity/Reproducibility	Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials	0	0	0
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	0	0	0
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =2, very consistent =3)	2	2	2
Generalizability	Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre =1, moderate likelihood i.e. multicentre with limited patient population or practice setting =2, high likelihood i.e. multicentre, heterogeneous patients, diverse practice settings =3.	2	2	2
Cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2	2
Feasible	Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU	2	2	2
Safety	Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm	2	2	2

* refers to formula containing fish oils, borage oils and antioxidants

4.1b(i) Composition of Enteral Nutrition: Fish Oils, Borage Oils and Antioxidants*

Question: Does the use of an enteral formula with fish oils, borage oils and antioxidants result in improved clinical outcomes in the critically ill adult patient?

Summary of evidence: There were 3 level 1 and 5 level 2 studies reviewed and 7 of these used Oxepa®, an enteral formula with fish oils, borage oils, antioxidants, vit. E, C, beta-carotene, taurine & L-carnitine as a continuous formula, one used the components of the same formula but administered it as a bolus (Rice 2011) . Of these, 6 studies used the special diets as treatments for patients with Acute Respiratory Distress Syndrome (ARDS)/Acute Lung Injury (ALI), one used the special diets prophylactically in multiple trauma/head injury patients (Kagan 2015) and one study looked at effects of the fish oil/borage oil formula on the healing of pressure ulcers (Theilla 2011).The earlier Moran 2006 study was replaced by the recent Grau-Carmona 2011 study and the earlier Miller 2005 study that was in abstract form was replaced by Elamin 2012. The INTERSEPT study (Pontes-Arruda 2011) was excluded as less than 50% patients were mechanically ventilated.

In the Rice study, participants were also randomized to a separate trial (EDEN study) comparing low vs full enteral nutrition in a 2X2 factorial design in which the control group received significantly more protein. For more for details on the low vs full enteral nutrition, refer to section *3.3 Intentional Underfeeding: Trophic Feeds.* Two studies used a fish oil only supplement; one as a bolus (Stapleton 2011) and another as soft gel capsules (Parish 2014). These studies are covered under the section *4.1(b-ii): Fish Oils.*

Since the delivery of the intervention through bolus vs continuous may affect blood levels (absorption), sensitivity analyses excluding the study that used bolus administration (Rice 2011) were done.

Mortality: When the data from the 8 studies that reported on mortality were aggregated, the use of Oxepa® and/or fish oil supplementation had no effect on mortality (RR 0.87, 95% CI 0.62, 1.22, p=0.41, heterogeneity I^2=50%; figure 1).). When a sensitivity analyses was done excluding the Rice 2011 study, the use of Oxepa® formula was associated with a significant reduction in 28 day mortality (RR 0.72, 95% CI 0.56, 0.92, p=0.008, heterogeneity I^2=0%; figure 2).

Infections: Three multicentre studies reported on ventilator associated pneumonia and found no significant differences between the groups (RR 1.07, 95% CI 0.82, 1.69, p=0.63, heterogeneity I^2=0%; figure 3).

LOS and Ventilator days: When the data from the 5 studies were aggregated, the use of Oxepa® /fish oil supplement showed no significant difference in the reduction of ICU length of stay (WMB -1.62, 95% CI -5.44, 2.19, p=0.40; figure 4). In two of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses and 1 study reported on ICU free days, showing a significant reduction in ICU free days with the use of fish oil supplementation (Rice 2011, p=0.04). When the data from the 4 studies were aggregated, the use of Oxepa®/fish oil supplementation was not associated with a significant reduction in ventilated days (WMD -2.91, 95% CI -7.44, 1.62, p=0.21; figure 5). In two of the studies, the data was not represented as means ± standard deviations, hence was not included in the meta-analyses (Grau-Carmona 2011 & Elamin 2012) and in 2 studies ventilator free days were reported. Rice

et al reported a significant reduction in vent free days in the fish oil group (p=0.02) while Elamin et al and Grau-Carmona et al reported no difference in ventilator dependent days (p=0.3 and p=0.4 respectively)

Other complications: The use of Oxepa® was associated with a significant reduction in number of new organ failures in 2 studies (Gadek 1999 p=0.018) (Pontes-Arruda 2006, p< 0.0010), and a significant reduction in MODS score after 28-days in one study (Elamin 2005, p<0.05). However, in another study (Grau-Carmona 2011), the median SOFA score was 9 (IQ range: 7-11) and the number of organ failures was similar in both groups. Kagan 2015 found no difference in the development of new organ failures (p=0.27). In two studies, Oxepa® was associated with an improvement in oxygenation, pulmonary static compliance and resistance (Gadek 1999, Singer 2006). There were no differences in GI events between the groups (p=0.82) in one study (Gadek 1999).

Conclusions:

1) Bolus supplementation of fish oil/borage oil/antioxidants vs placebo has no effect on mortality, infections in critically ill patients, ventilator free days or ICU length of stay.
2) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants administered continuously is associated with a significant reduction in 28 day mortality in patients with ALI/ARDS

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating enteral formula with fish oils, borage oils and antioxidants in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)		Infections # (%)‡	
				Fish Oils	Standard	Fish Oils	Standard
1)Gadek 1999	ARDS patients from 5 ICUs N=146	C.Random: yes ITT: yes Blinding: yes (13)	Fish oil, borage oil +antioxidants Oxepa ®) vs standard high fat, low CHO (Pulmocare†) Received 9.8 gms/day fish oils (EPA+DHA††)	28-day 11/70 (16)	28-day 19/76 (25)	NR	NR
2)Singer 2006	ARDS and acute lung injury patients N=100	C.Random: yes ITT: yes Blinding: no (11)	Fish oil, borage oil +antioxidants Oxepa ®) vs standard high fat, low CHO (Pulmocare†)	28-day 14/46 (30)	28-day 26/49 (53)	NR	NR
3) Pontes-Arruda 2006	Severe sepsis or septic shock patients with ALI from 3 ICUs N=165	C.Random: not sure ITT: yes* Blinding: double (7)	Fish oil, borage oil +antioxidants ((Oxepa ®) vs standard high fat, low CHO (Pulmocare†). Received 7.1 gms/day of fish oils ((EPA+DHA††)	28-day 26/83** (31)	28-day 38/82** (46)	NR	NR
4) Rice 2011	ALI patients, mechanically ventilated from 44 ICUs N=272	C.Random: yes ITT: yes Blinding: yes (13)	Fish Oil supplement (6.84g EPA, 3.4g DHA, 5.92g GLA) with 5.8 gms protein, Vit C, E, beta-carotene, selenium 120 ms boluses X2 day vs. isovolemic control solution (no EPA/DHA) with 52 gms protein, Both groups receieved EN feeding.	60-day 38/143 (27)	60-day 21/129 (16)	VAP 10/143 (7) Bacteremia 16/143 (11)	VAP 10/129 (8) Bacteremia 14/129 (11)
5) Grau-Carmona 2011	Septic patients with ALI or ARDS N=160	C.Random: no ITT: no Blinding: yes (5)	Fish oil, borage oil + antioxidants (Oxepa ®) 52.5g Pro/L vs. isocaloric, isonitrogenous, high protein formula (Ensure Plus) 66.6g Pro/L isocaloric	28-day 11/61 (18)	28-day 11/71 (16)	VAP 32/61 (53)	VAP 34/71 (48)
6) Thiella 2011	ICU patients with pressure ulcers N=40	C.Random: no ITT: yes Blinding: no (5)	Fish oil, borage oil + antioxidants 66.1 gm pro/day (Oxepa ®) vs. Isocaloric/isonitrogenous polymeric formula (Jevity) 65.1 gm pro /day	NR	NR	NR	NR

7) Elamin 2012	ARDS patients from 2 ICUs N = 22	C.Random: yes ITT: no Blinding: double (7)	EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs EN formula of standard high fat vs low CHO (Pulmocare)	28-day 0/9 (0)	28-day 1/8 (12.5)	NR	NR
8) Kagan 2015	Multiple trauma or head injury patients from a single ICU N=120	C.Random: yes ITT: yes Blinding: double (10)	EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs EN formula of standard high fat/low CHO (Pulmocare)	28-day 8/62 (13)	28-day 5/58 (8)	VAP 25/62 (40%) Wound infection 12/62 Bacteremia 14/62 New organ failure 31/62	VAP 22/58 (38%) Wound infection 10/58 Bacteremia 3/58 New organ failure 23/58

Table 1. Randomized studies evaluating enteral formula with fish oils, borage oils and antioxidants in critically ill patients (continued)

Study	Length of Stay (days)		Duration of Ventilation (days)		Other	
	Fish Oils	Standard	Fish Oils	Standard	Fish Oils	Standard
1) Gadek 1999	ICU*** 11 ± 7.53 (70) Hospital*** 27.9 ± 17.57 (70)	ICU*** 14.8 ± 11.03 (72) Hospital*** 31.1 ± 13.15 (72)	9.6 ± 7.94 (70)***	13.2 ± 11.88 (72)***	New Organ Failures 7/70 (10)	19/76 (25)
2) Singer 2006	ICU 13.5 ± 11.8 (46)**	ICU 15.6 ± 11.8 (49)**	12.1 ± 11.3 (46)**	14.7 ± 12 (49)**		
3) Pontes-Arruda 2006	ICU 17.2 ± 4.9 (55)**	ICU 23.4 ± 3.5 (48)**	14.64 ± 4.3 (55)**	22.19 ± 5.1 (48)**	New Organ Dysfunction 38%	81%
4) Rice 2011	ICU Free Days 14.0 ±10.5	ICU Free Days 16.7 ± 9.5	Ventilator-free Days 14.0 ±11.1	Ventilator-free Days 17.2 ±10.2	Non-pulmonary Organ Failure-free Days 12.3 ± 11.1	15.5 ± 11.4
5) Grau-Carmona 2011	ICU 16 (11-25)	ICU 18 (10-30)	10 (6-14) p=0.4	9 (6-18)	Nutritional Intake 1 (kcal/day) 718 (1189-1965) p=0.5	1599 (1351-1976)
6) Thiella 2011	ICU 26.1 ± 14.2 (20)	ICU 21.2 ± 9.1 (20)	NR	NR	Change in Pressure Ulcers Scale 1.5 p≤0.05	0.3

7) Elamin 2012	ICU 12.8	ICU 17.5	6.7	8.2	MODS Score at 7 days Lower in fish oil group (p<0.06) MODS Score at 28 days Lower in fish oil group (p<0.05)
8) Kagan 2015	ICU 19.5 ± 15.3 (62) Hospital 33.1 ± 25.7 (62)	ICU 16.4 ± 11.3 (58) Hospital 27.1 ± 17.3 (58)	17 ± 15.1	13.6 ± 10.7	New organ failure 31/62 23/58, p=0.27

† Fat source of Pulmocare varied between the studies: Gadek 1999 study used product that had 97 % corn oil, 3% soy lecithin; Singer 2006 and Pontes-Arruda 2006 used product that had 14 % corn oil, 20% MCT,56 % canola oil.

†† EPA: Eicosapentanoic acid, DHA: docosahexanoic acid

* data on mortality is Intent-to–treat

** data obtained from authors

***values computed from mean ± SE to obtain mean ± SD

C.Random: concealed randomization

ITT: intent to treat

assumed to be hospital mortality unless specified

‡ refers to the # of patients with infections unless specified

± ( ) : mean ± Standard deviation (number)

NR: not reported

Figure 1. Mortality

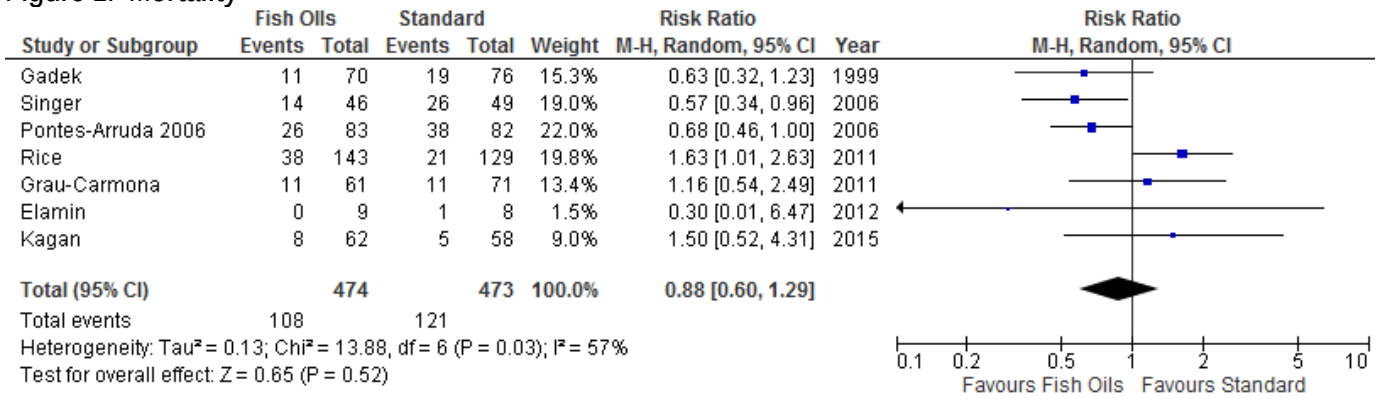

Figure 2. Mortality (without Rice 2011)

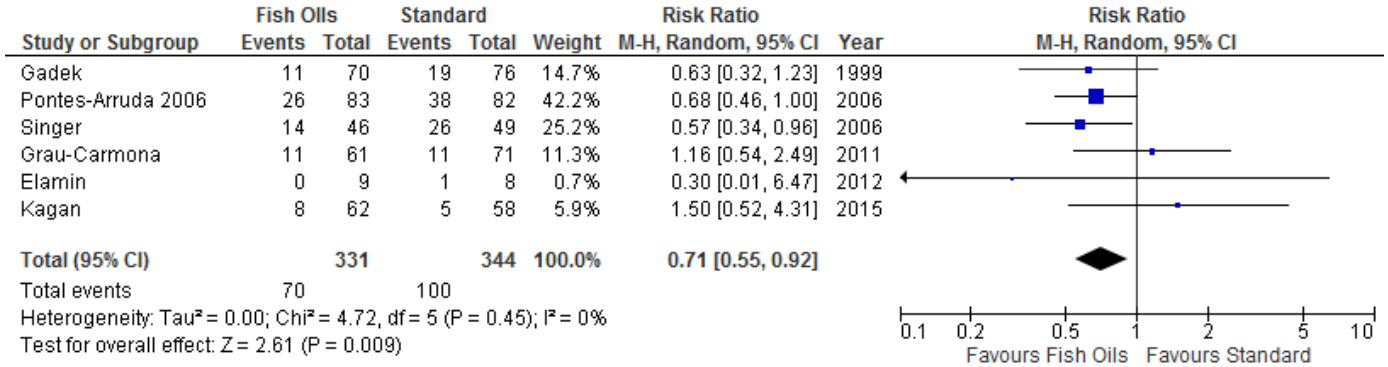

Figure 3. Ventilator Associated Pneumonia

Study or Subgroup	Fish Oils Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grau-Carmona	32	61	34	71	57.4%	1.10 [0.78, 1.54]	2011
Rice	10	143	10	129	9.4%	0.90 [0.39, 2.10]	2011
Kagan	25	62	22	58	33.3%	1.06 [0.68, 1.66]	2015
Total (95% CI)		**266**		**258**	**100.0%**	**1.07 [0.82, 1.38]**	
Total events	67		66				

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

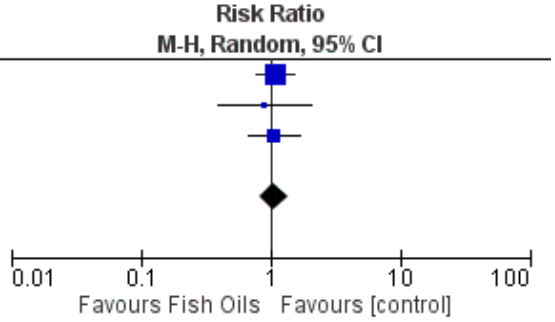

Figure 4. ICU Length of Stay

Study or Subgroup	Fish Oils Mean	SD	Total	Standard Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gadek	11	7.53	70	14.8	11.03	72	22.9%	-3.80 [-6.90, -0.70]	1999
Pontes-Arruda 2006	17.2	4.9	55	23.4	3.5	48	25.7%	-6.20 [-7.83, -4.57]	2006
Singer	13.5	11.8	46	15.6	11.8	49	19.0%	-2.10 [-6.85, 2.65]	2006
Thiella	26.1	14.2	20	21.2	9.1	20	13.4%	4.90 [-2.49, 12.29]	2011
Kagan	19.5	15.3	62	16.4	11.3	58	18.9%	3.10 [-1.69, 7.89]	2015
Total (95% CI)			**253**			**247**	**100.0%**	**-1.62 [-5.44, 2.19]**	

Heterogeneity: Tau² = 14.02; Chi² = 21.22, df = 4 (P = 0.0003); I² = 81%
Test for overall effect: Z = 0.83 (P = 0.40)

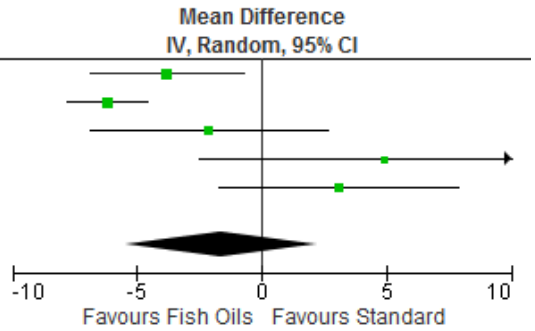

Figure 5. Duration of Ventilation

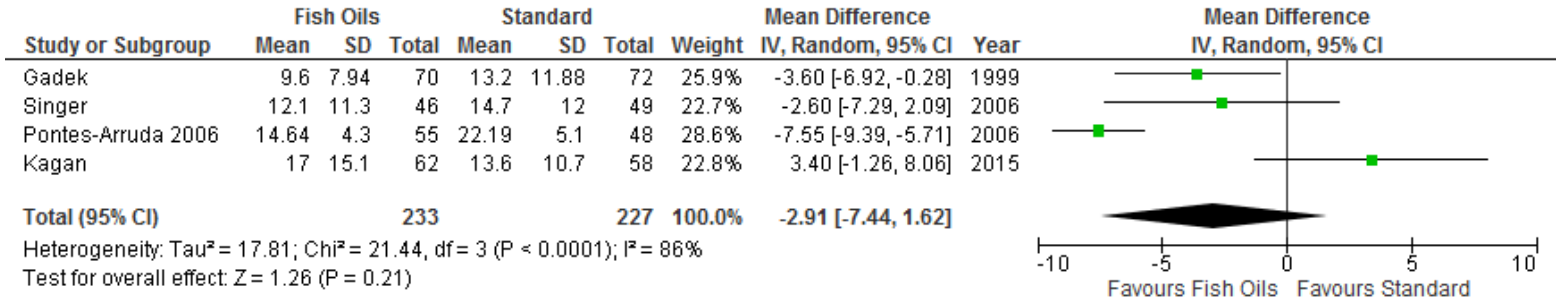

Table 2. Composition of Fish Oil Containing Formulas Compared to Standard

These values represent the version of these products produced for sale in the United States.
Products sold in other countries may have other nutrient values, depending on country specific requirements.

	Oxepa	Pulmocare*	Jevity 1.5	
Cal/ml	1.5	1.5	1.5	
Grams fat/liter	93	93	49.8	
Grams n-3/liter	10.15	4.8	2.4	
Grams alpha-linolenic acid/liter	3.1	4.8	2.4	
Grams EPA/liter	4.6	0	0	
Grams DHA/Liter	2.0	0	0	
Grams n-6/liter	18.4	18.4	13.3	
Grams linoleic acid/liter	14.5	18.4	13.3	
Grams GLA/liter	4.29	0	0	
Grams n-9 per liter	21.7	39	17.2	
Grams oleic acid/liter	21.7	39	17.2	
Grams of MCT oil/liter	23.5 grams (25% of fat blend)	18.6 grams (20% of fat blend)	9.46 grams (19% of fat blend)	Recommended
n6:n3 ratio	1.8:1	3.8:1	5.5:1	2:1 to 4:1
n3:n6 ratio	0.5:1	0.26:1	0.18:1	
Oil blend ingredients	31.8%Canola oil, 25% MCT oil, 20% fish oil, 20%borage oil, 3.2% soy lecithin	55.8%Canola oil, 20%MCT oil, 14%corn oil, 7%high oleic acid safflower oil, 3.2% soy lecithin	Canola oil, MCT oil and corn oil, soy lecithin	

EPA: Eicosapentanoic acid DHA: docosahexanoic acid GLA: gamma linoleic acid

**Fat source of Pulmocare varied between the studies: Gadek 1999 study used product that had 97 % corn oil, 3% soy lecithin; Singer 2006 and Pontes-Arruda 2006 used product that had 14 % corn oil, 20% MCT,56 % canola oil.*