

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 7 level 2 studies reviewed and 8 of these used Oxepa®, an enteral formula with fish oils, borage oils, antioxidants, vitamin E and C, beta-carotene, taurine & L-carnitine as a continuous formula. One used the components of the Oxepa® formula but administered them as a bolus (Rice 2011). One study used an omega 3 enriched EN formula and gave additional supplemental omega 3 and antioxidants (Hosny 2014). Of the included studies, 7 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), one study looked at effects of the fish oil/borage oil formula on the healing of pressure ulcers (Theilla 2011) and one studied septic patients (Hosny 2014). 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 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 9 studies that reported on mortality were aggregated, the use of Oxepa® and/or fish oil supplementation had no effect on mortality (RR 0.91, 95% CI 0.65, 1.27, $p=0.58$, heterogeneity $I^2=49%$; figure 1). When a sensitivity analyses was done excluding the Rice 2011 study, the use of fish oil, borage oil and antioxidants was associated with a significant reduction in mortality (RR 0.75, 95% CI 0.59, 0.96, $p=0.02$, heterogeneity $I^2=4%$; 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 7 studies were aggregated, the use of Oxepa® /fish oil supplement showed a trend toward a reduction of ICU length of stay (WMB -2.60, 95% CI -5.43, 0.22, $p=0.07$; figure 4). In two of the studies, the data was not represented as means \pm 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 5 studies were aggregated, the use of Oxepa®/fish oil supplementation was associated with a significant reduction in ventilated days (WMD -3.49, 95% CI -6.33, -0.66, $p=0.02$; figure 5). In three of the studies, the data was not represented as means \pm standard deviations, hence was not included in the meta-analyses (Grau-Carmona 2011, Elamin 2012, Hosny 2014) and in 2 studies ventilator free days were reported. Rice et al

reported a significant reduction in ventilator free days in the fish oil group ($p=0.02$), Hosny et al saw a trend in reduction of ventilated days ($p=0.115$) 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) 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 reduction in mortality in patients with ALI/ARDS or sepsis.
- 2) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants has no effect on infectious complications.
- 3) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants may be associated with a reduction in ICU LOS.
- 4) When compared to a standard/high fat formula, the use of an enteral formula with fish oil/borage oil and antioxidants is associated with a reduction in ventilator dependent days.

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 received 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) Hosny 2014 | ICU patients with sepsis. Single centre. N=75 | C.Random: no ITT: no Blinding: no (7) | High dose omega 3 + antioxidants medications + EN enriched with omega 3s (14.2% of lipid content) vs control group (standard EN, no meds). | 28-day 8/25 (32) | 28-day 10/25 (40) | NR | NR |
| 9) 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 |
| 10) Shirai 2015 | Mechanically ventilated ICU patients. Single centre. N=46 | C.Random: no ITT: yes Blinding: single (11) | EN formula containing fish oil, borage oil and antioxidants (Oxepa) vs isocaloric polymeric formula (Ensure) | 60-day 3/23 (13) | 60-day 3/23 (13) | NR | NR |

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) | 9 (6-18) | Nutritional Intake 1 (kcal/day) 718 (1189-1965) 1599 (1351-1976) p=0.5 |
| 6) Thiella 2011 | ICU 26.1 ± 14.2 (20) | ICU 21.2 ± 9.1 (20) | NR | NR | Change in Pressure Ulcers Scale 1.5 0.3 p≤0.05 |
| 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) Hosny 2014 | ICU 11.6 ± 6.1 (25) | ICU 13.9 ± 4.2 (25) | 6.7 ± 3.8 | 10.9 ± 6.3 | Diarrhea 20% 16% |
| 9) 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 |
| 10) Shirai 2015 | ICU Mean, (SE, 95% CI) 17.63 (1.70, 14.30-20.97) SD = 8.15*** | ICU Mean, (SE, 95% CI) 25.87 (2.6, 20.81-30.94) SD=12.47*** | Mean, (SE, 95% CI) 13.61 (1.00, 11.66-15.56) SD=4.80*** | Mean, (SE, 95% CI) 17.777 (1.81, 14.21-21.33) SD=8.68*** | Nutritional intake, day 7, kcal/kg/d 18.78 (18.12-20.21) 19.48 (15.73-20.68) Nutritional intake, day 14, kcal/kg/d 24.22 (23.32-25.9) 24.32 (22.67-25.75) Nutritional intake, day 7, g/kg/d 0.781 (0.7-0.837) 0.613 (0.529-0.683) Nutritional intake, day 14, g/kg/d 0.988 (0.933-1.063) 0.81 (0.749-0.863) |

† 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

ITT: intent to treat

± () : mean ± Standard deviation (number)

** data obtained from authors

assumed to be hospital mortality unless specified

NR: not reported

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

‡ refers to the # of patients with infections unless specified

C.Random: concealed randomization

Figure 1. Mortality

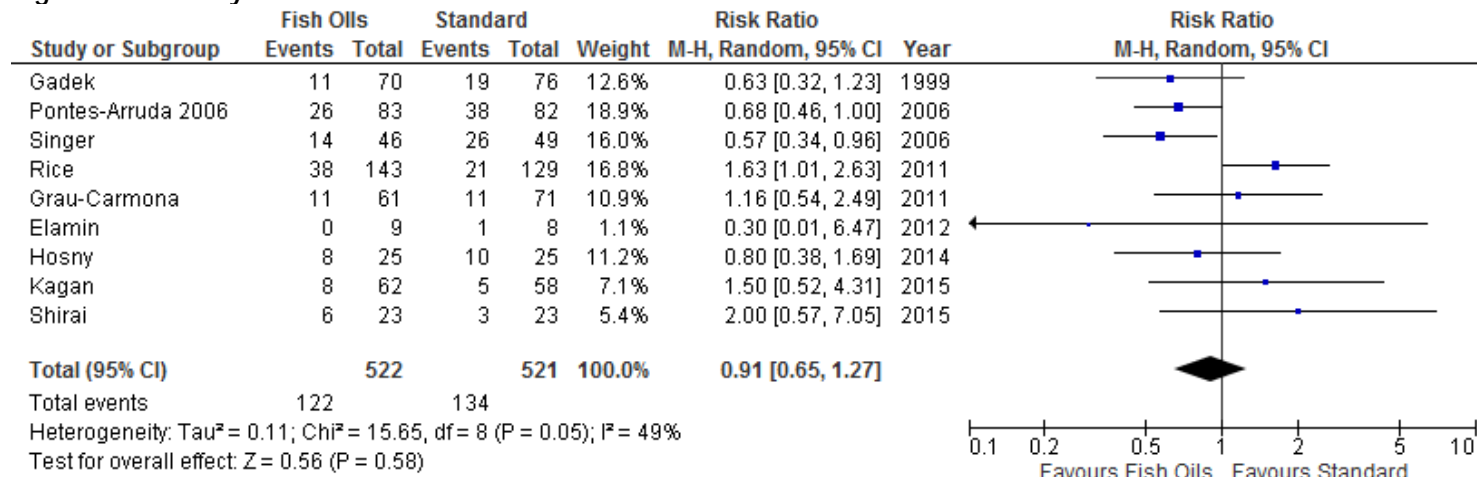


Figure 2. Mortality (without Rice 2011)

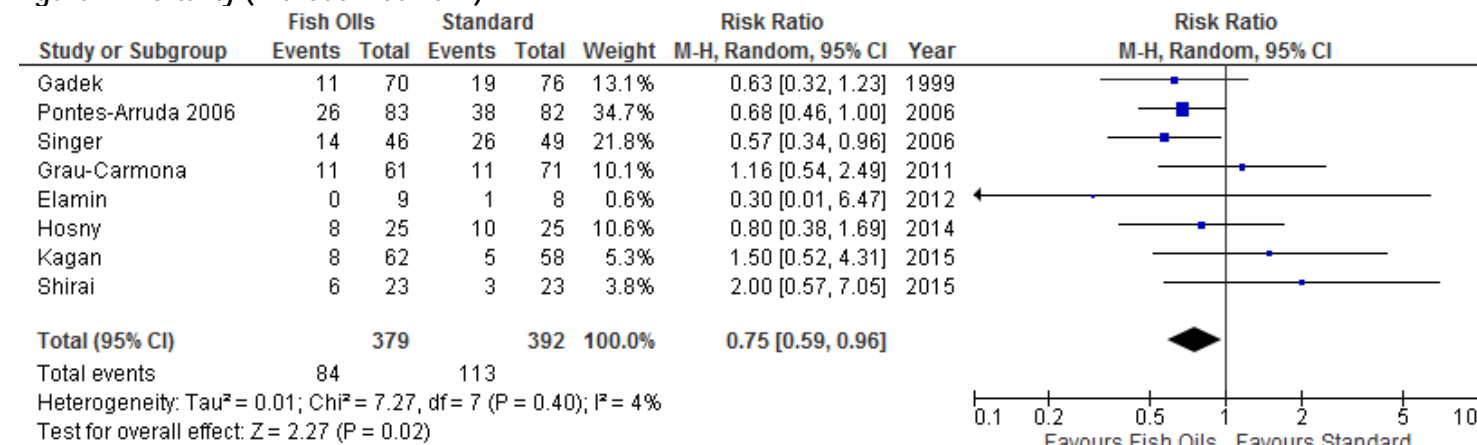


Figure 3. Ventilator Associated Pneumonia

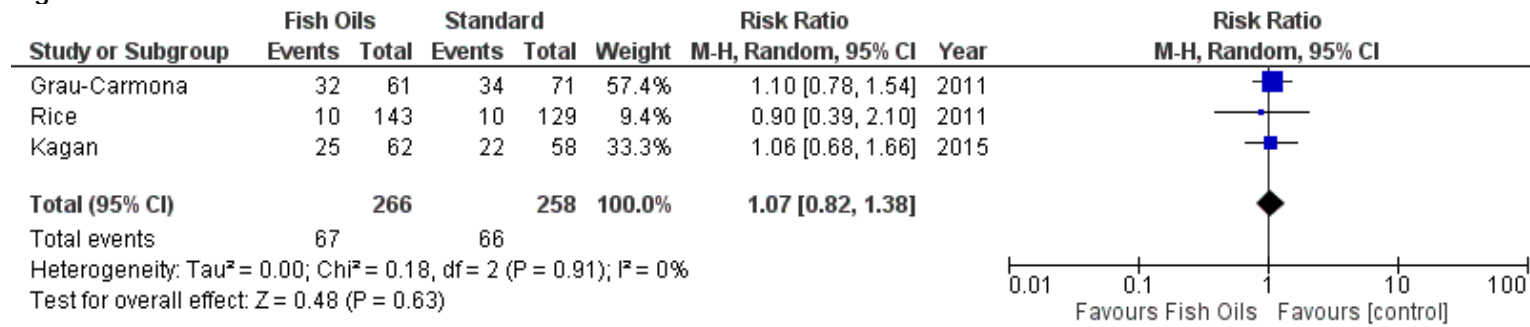


Figure 4. ICU Length of Stay

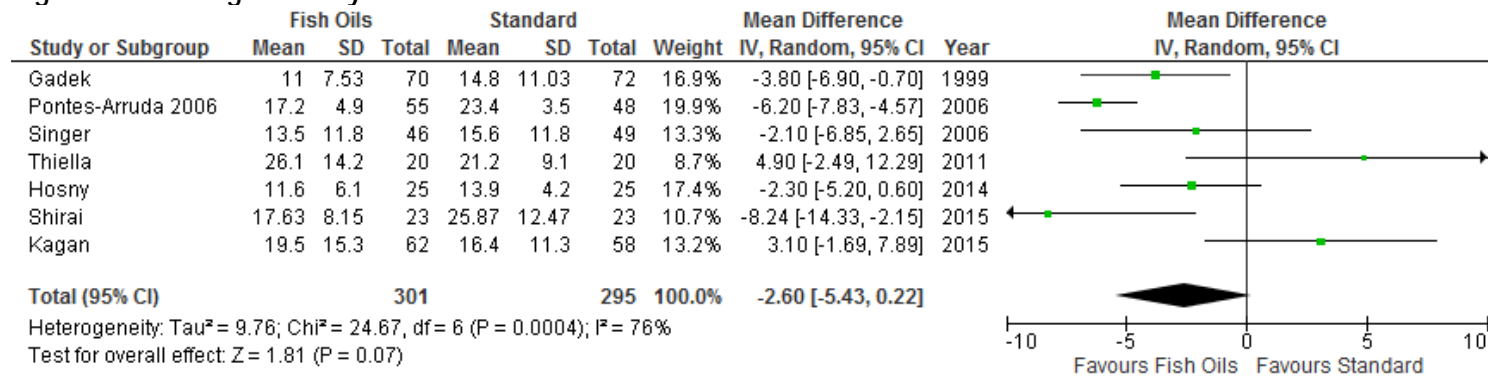


Figure 5. Duration of Ventilation

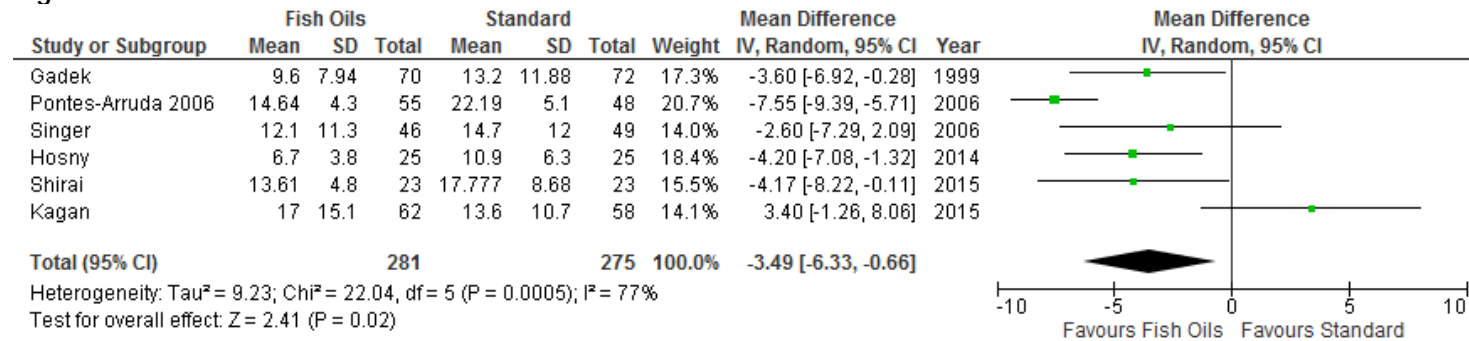


Table 2. Composition of Fish Oil Containing Formulas Compared to Standard

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.