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Background Paper on Fat and Fatty Acid Requirements during Pregnancy and Lactation

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Introduction

The purpose of this background paper is to review evidence relevant to estimating the dietary essentiality of specific fatty acids in the diets of pregnant and lactating women, and when possible to provide guidance for specific dietary levels. Evidence is emphasized according to the hierarchy outlined in the background paper provided to consultancy members [Smit et al., 2009], especially section 5: 'Choice of criteria, evidence, and dietary reference intakes'.

Pregnancy and lactation imposes special nutritional needs on the mother-fetus/infant. With respect to fat, the overwhelming majority of research in the past 2 decades on dietary fat in the perinatal period has focused on nutritional needs for polyunsaturated fatty acids (PUFA), and of these docosahexaenoic acid (DHA) and arachidonic acid (AA) have received the most attention.

Pregnancy first imposes nutritional demands on the mother for energy and for components to grow the placenta, and, soon afterward, the fetus. Maternal nutrition has long been recognized as important for both perinatal health and for the long-term health of the infant. Deficiencies in placental growth due to frank malnutrition have long been recognized as harmful to the infant, and some of the mechanisms by which fetal and infant nutrition influence chronic disease have been investigated recently [Barker, 2007]. Specific nutrients have also long been recognized as being of possible importance to long-term infant health. With respect to fatty acid nutrition, consumption of various oils during the last week of pregnancy was found to permanently program avoidance behavior in rats [Messeri et al., 1975] despite the postnatal brain growth spurt in this species, which is consistent with several other studies demonstrating perinatal effects of PUFA nutrition on behavior [Borgman et al., 1975; Lamptey and Walker, 1978]. Similarly, cholesterol intake in infancy was hypothesized to program cholesterol levels in later life, first supported by data in rats [Reiser and Sidelman, 1972; Jensen et al., 1978]. More recently, baboon [Mott et al., 1990] and human studies [Owen et al., 2002] indicate that breast feeding has positive effects on the infant's later cholesterol physiology, and in addition is consistently associated with later cognitive benefits [Schack-Nielsen and Michaelsen, 2006]. Notably, experimental studies of the influence of perinatal nutrition on chronic disease development in humans are impossible due to ethical and practical considerations. However, evidence from randomized controlled trials (RCT) that evaluate acute outcomes, reviewed below, are fully consistent with the hypothesis that long-chain PUFA (LCPUFA) nutrition is a key factor linking breast feeding to the infant's CNS development and the mother's mental health.

Specific health conditions in pregnancy influence either the mother or the infant, or both. The most unambiguous evidence tends to be associated with health con-

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sequences that develop, or can be treated, on the time scale of clinical trials. Many outcomes associated with the reproductive period extend for many years. Further, studies of low-risk populations are more easily planned and executed than those of pregnant and lactating women and infants, who are among the most vulnerable of study participants. For these reasons, development of evidence in these groups is challenging despite, or alternatively because of, the very high priority placed on these groups.

The major functional outcomes that have been studied in the infant are visual and cognitive maturity, immune function, and growth. For the mother, glucose tolerance, preeclampsia, and psychiatric health have been considered, and for the mother-offspring pair, maintenance of normal pregnancy to term has been of the most interest with respect to fat and fatty acid intake.

Dietary Fat Intake in Pregnancy and Lactation

The dietary proportion of calories as fat is relevant to caloric density, which in turn is relevant to the increasing incidence of obesity and attendant metabolic issues. There are few studies looking at the relationship of dietary fat intake and classes of fatty acids, assessed by questionnaires, on gestational diabetes mellitus (GDM) or impaired glucose intolerance (IGT). The relation between macronutrient intake and the development of glucose intolerance during pregnancy has been poorly examined. In one study, dietary intake during the second trimester was assessed with a food frequency questionnaire (FFQ), and women were classified into GDM, IGT or normal glucose tolerance [Saldana et al., 2004]. Adding 100 kcal from carbohydrates to the diet was associated with a 12% decrease in risk of IGT and a 9% decrease in risk of GDM, and substituting fat for carbohydrates resulted in a significant increase in risk of both IGT and GDM, suggesting that excess of fat intake during pregnancy may be detrimental in terms of GDM and IGT. A recent prospective study in the eastern USA compared first trimester diet studied with a FFQ with risk for development of GDM or IGT at weeks 26–28. No significant relationship was found between the risk of GDM and intake of total fat, saturated fat, PUFA, or *trans* fat [Radesky et al., 2008]. A significant relationship with n–3 PUFA (per 300 mg/day increment) was found, but ascribed to a chance finding. A cross-sectional study of pregnant women in Shanghai compared diet assessed by 24-hour recall with existing IGT and GDM. Total fat intake was similar to a normal group, but a highly significant relationship was found between IGT/GDM and reduced PUFA intake, and while no distinction between n–3 and n–6 was possible, the authors speculated that there was little likelihood of a difference between groups [Wang et al., 2000]. A retrospective study in northern Italy restricted to women with GDM or IGT showed that intake of saturated fat was positively related to the risk of GDM or IGT in women with conventional risk factors. Among those with no conventional risk factors, intake of saturated fat was positively correlated with gestational hyperglycemia, while PUFA consumption was correlated with lower risk [Bo et al., 2001]. These studies are suggestive of a relationship between intake of specific fats and development of abnormalities in glucose metabolism, suggesting that pregnant women at the higher end of PUFA intake are less likely to have impairment of glucose metabolism in pregnancy. A similar association between dietary elongated n–3 fatty acids and the risk of preeclampsia and gestational hypertension has been suggested, but must to be confirmed by further studies [Oken et al., 2007].

Dietary *trans* fatty acids (TFA) are associated with negative health conditions in pregnancy. TFA is a generic term that refers to partially hydrogenated vegetable oil (PHVO) containing a broad distribution of monounsaturated fatty acid (MUFA) with *trans* double bonds, unusual *cis* isomers, and *trans* double bonds in higher unsaturates; the latter, or unknown compounds, may be responsible for the hypercholesterolemic effects of PHVO [Tyburczy et al., 2009]. Erythrocyte TFA, reflective of diet, were strongly associated with preeclampsia in a case-control study of pregnant women in the US [Williams et al., 1998] and in Zimbabwe [Mahomed et al., 2007], though no relationship with dietary TFA, assessed with a FFQ, was found in another US study [Oken et al., 2007]. Dietary TFA, assessed by FFQ, have recently been associated with ovulatory infertility [Chavarro et al., 2007], fetal loss [Morrison et al., 2008], lowered birth weight and head circumference [Hornstra et al., 2006; van Eijsden et al., 2008]. TFA are at similar concentrations in the maternal and fetal circulations at birth, showing that the fetus is exposed to maternal TFA [Koletzko and Müller, 1990]. It has long been known that dietary TFA intake among pregnant and lactating women is directly related to the breast milk TFA [Aitchison et al., 1977; Craig-Schmidt et al., 1984]. There is some evidence that they are inversely related to PUFA in breast milk, which may compromise benefits [Innis and King, 1999]. Combined with experimental data [Albuquerque et al., 2006; Morrison et al., 2008; Pisani et al., 2008a, 2008b],

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sufficient data exist on TFA to warrant caution against consumption of foods with PHVO in pregnancy and lactation, though the data in humans are largely associational and do not permit setting of quantitative targets.

Conceptus (Placenta and Fetal) PUFA

In the first weeks of pregnancy, the fetal demands for structural fat are expected to be small compared to the mother's stores. The placenta is primarily a vascular organ facilitating material transport between mother and fetus. It grows rapidly in early pregnancy and continues to grow to term, and has a high requirement for phospholipids as structural fat, which makes up about 88% of placental lipids [Klingler et al., 2003]. Placental unsaturated phospholipids are dominated by AA, which appear at a several-fold greater concentration than DHA and other PUFA. AA precursors linoleic acid (LA) and dihomo-γ-linolenic acid (DGLA) are also at higher concentrations than n–3 precursors [Bitsanis et al., 2005]. Biosynthesis of AA from its primary dietary precursor LA is thought to be rapid because the 3 enzymatic steps (Δ6-desaturation, elongation, Δ5-desaturation) are usually considered to be rapid compared to the 7 steps involving 2 organelles in the accepted pathway for DHA biosynthesis. An alternative pathway to AA has recently been shown to be possible via Δ8-desaturation of 20:2n–6, mediated by the fatty acid desaturase 2 (FADS2) gene product, when this substrate is available [Park et al., 2009]. In normal pregnancy, there is no evidence that dietary n–6, including AA, is inadequate.

Increases in the concentration of LCPUFA from maternal tissues to fetal circulation to fetal tissues, referred to as biomagnification, have long been known [Crawford et al., 1976]. Longitudinal data on maternal and umbilical blood phospholipid fatty acid composition indicate that DHA as a percent of total fatty acids in the fetal blood increases dramatically after 20 weeks gestation [Al et al., 1995, 2000]. In vitro and in vivo experiments support a highly selective fatty acid transfer through the placenta, with the order of preference being DHA>AA>α-linolenic acid (ALA) and LA [Ruyle et al., 1990; Haggarty et al., 1999]. A marked increase from the umbilical artery to vein (28%[1]; 2.2 μg/10^9 RBC) was observed for red blood cell (RBC) DHA in human cord blood, but not for plasma DHA. Most other fatty acids showed similar non-significant trends, indicating that fetal RBC play a role in the transport of DHA and possibly other fatty acids [Ruyle et al., 1990]. Fetal venous RBC had nearly double the DHA than maternal venous RBC.

The fetal and infant CNS has long been known to be rich in fat, and especially DHA and AA. The human brain growth spurt starts around the 28th week of gestation and continues to 1 year [Dobbing and Sands, 1979], while the demand for DHA and AA continues to 2 years of age [Martinez, 1992]. In humans, AA dominates in early in utero brain growth, and later DHA concentrations dominate. The synapses are especially rich in DHA, as are all regions of gray matter [Diau et al., 2005]. Animal studies show that DHA is obtained from milk postpartum and enhances CNS plasma membrane concentrations [Arbuckle and Innis, 1993; Hsieh et al., 2007]. Infants fed formula without DHA and AA have lower CNS DHA compared to those who are breastfed [Farquharson et al., 1992; Makrides et al., 1994], consistent with these animal results. DHA and AA are present in human milk. DHA concentrations are variable and respond to dietary factors, while AA is more constant [Yuhas et al., 2006; Brenna et al., 2007]. It is clear, therefore, that the pregnant and lactating mother provides DHA and AA to the developing fetus via preferential placental transfer and later via breast milk. Both must come from 1 of 3 sources: maternal stores, biosynthesis from precursors, or preformed from the maternal diet.

It is likely that initiation of enhanced LCPUFA intake at any stage in pregnancy or lactation can at least partially make up for previously low intakes prior to conception and in the first weeks of gestation, unlike some nutrients such as folate, for which intake around the time of conception is crucial. PUFA demands attendant to pregnancy and lactation to support the placenta and fetus/infant are substantial. In the normal-term infant, total body DHA is estimated at 3.8 g at birth [Cunnane et al., 2000], so accretion of DHA must average (3,800 mg/280 days) 14 mg/day through gestation. An earlier estimate of total n–3 PUFA accretion in term infants in the last trimester was primarily for adipose, and was 67 mg/day; of this, most is DHA [Clandinin et al., 1981]. A re-evaluation of the fetal n–3 PUFA accretion during the last trimester suggests an even higher accretion rate of 75 mg/day, which translates into an accretion rate of 34.1 mg per kg body weight per day [Lapillonne and Jensen, 2009]. Fetal accretion is low in the first half of gestation, and the bulk of demands for DHA are in the final 12 weeks as the brain and adipose rapidly expand. It is estimated that 65% of the n–3 fatty acids ac-

[1] '%' applied to fatty acid composition refers to 'weight for weight' (%, w/w), unless specified otherwise.

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cumulate in the fetal adipose tissue, 30% in lean mass, and only 3.9% in the brain and 0.7% in the liver. Since it is not known whether dietary DHA is preferentially directed to the brain, its accumulation in organs other than the CNS should be taken into consideration when estimating DHA requirements for preterm infants. PUFA storage in maternal adipose and other tissue is substantial compared to demands, and thus expressing requirements on a daily basis throughout pregnancy is appropriate

The normal breastfed infant accretes 1,900 mg DHA in the first 180 days of life (11 mg/day), whereas infants fed formula with no DHA and AA lose 900 mg DHA largely from adipose [Cunnane et al., 2000]. Many studies show that dietary precursors are converted to DHA very inefficiently; thus, DHA is poorly synthesized by adult humans. ALA itself is oxidized at the highest rate known among fatty acids, around 60% in the first days after consumption in adults [Brenna, 2002], and more than a dozen studies show that blood DHA levels in adults can be raised only with consumption of preformed DHA [Brenna, 2002; Plourde and Cunnane, 2007; Brenna et al., 2009]. Unlike adults, infant blood DHA rises with increased ALA status, and thus infants appear to be more efficient converters than adults [Clark et al., 1992; Jensen et al., 1996]. Recent data are consistent and indicate that biosynthesis is significant in preterm newborns and falls off within months of birth [Carnielli et al., 2007]. However, other isotope measurements indicate a wide range of biosynthetic capability among human infants. Though these studies are unable to establish whether infants can meet their requirements for DHA by biosynthesis from ALA, they show that DHA biosynthetic activity is undetectable for some infants [Uauy et al., 2000]. These infants would appear to be most vulnerable to a low intake of LCPUFA from breast milk with low DHA or by infant formula not containing DHA. There is evidence that preterm and term infants with improved LCPUFA status at birth have improved status at term post-conceptual age, suggesting that improved maternal DHA status may advantage the newborn [Foreman-van Drongelen et al., 1995; Guesnet et al., 1999].

PUFA Biosynthesis and Neural Function

Animal studies primarily in rats appearing in the 1960s showed that all the n–3 and n–6 PUFA can be synthesized from the 18 carbon precursors LA (18:2) and ALA (18:3). These in turn can be synthesized from 16 carbon precursors in vivo [Cunnane et al., 1995], verifying many in vitro studies demonstrating that the crucial part of the molecule that must be obtained from the diet is the homoallylic polyunsaturated moiety between the terminal methyl and the n–9 position, where n equals the total number of carbon atoms in the molecule.

Essential fatty acid deficiency studied in experimental animals by deletion of all unsaturated fatty acids, either by the use of fat-free diets or by fully hydrogenated fats, produces a scaly dermatitis and reproductive impairment that can be corrected by addition of small amounts of LA or PUFA mixtures such as lard. The symptoms are often ascribed mainly to LA, but more recent data indicate that LA and ALA can partially compensate for the absence of the other [Cunnane and Anderson, 1997; Bazinet et al., 2003], while having distinct and apparently indispensable functions. Human deficiency conditions of combined LA and ALA have been described in an infant on total parenteral nutrition, and ALA alone in an adult [Holman, 1998].

Compelling evidence derived from controlled feeding studies in healthy humans, including voluntary transgender (female to male, and male to female) participants, shows that women have a greater DHA status, measured in cholesterol esters, and this is due to estrogenic effects [Giltay et al., 2004a, b]. Experimental rat data have recently shown that capacity for DHA synthesis from ALA, the expression of related enzymes in the liver, and the mRNA expression of FADS1 (Δ5-desaturase) and FADS2 (Δ6- and Δ8-desaturase) genes are, respectively, 3.8 and 2.5 times greater in females than males, and that the Δ5-desaturase protein was higher in female livers (+50%). In contrast, no gender difference was observed in the cerebral cortex [Extier et al., 2009]. It is also likely that blood lipid and breast milk fatty acids in pregnancy and lactation are influenced by genetic variants, as has been demonstrated recently for the FADS1 and FADS2 gene [Xie and Innis, 2008]. These data are consistent with stable isotope tracer studies suggesting high inter-individual variation in DHA biosynthesis, but also greater DHA biosynthesis in women than in men [Burdge and Calder, 2005; Pawlosky et al., 2007]. Levels of breast milk DHA in vegans are less than half that of control omnivores [Sanders and Reddy, 1992] and similar to reported global minima in breast milk DHA [Brenna et al., 2007]. It is apparent, however, that vegans maintain basal DHA levels sufficient to avoid frank deficiency, and thus DHA biosynthesis is more efficient that that of omnivores, for whom ALA or eicosapentaenoic acid (EPA) supplementation does not increase plasma DHA [Brenna et al., 2009]. There is evidence that maternal DHA status is reduced after pregnancy, raising concern over a need to maintain levels in the case of consecutive closely spaced pregnancies [Hornstra, 2000].

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Accumulating biochemical evidence clearly shows that n–6 and n–3 PUFA serve as precursors to distinct oxygenated lipids with signaling function in many different processes, collectively termed eicosanoids (for 20-carbon compounds) and docosanoids (for 22-carbon compounds), active at low concentrations. Moreover, the specific and conserved PUFA composition of the CNS, dominated by high concentrations of DHA and AA [Diau et al., 2005] and the high DHA levels in the retina dominated by DHA [Benolken et al., 1973; Neuringer et al., 1986; Diau et al., 2003] suggest a structural role in membranes probably related to the efficiency of G-protein-coupled signaling [Gawrisch and Soubias, 2008] as well as other functions. For these reasons, neural tissue, particularly the retina, has been a focus of studies aimed at establishing evidence for optimal infant neural development based on perinatal PUFA intake.

LCPUFA Supplementation Trials and LCPUFA Status

Supplementation studies are valuable as a guide to the biochemical and physiological effects of a minimal change in the supply of a dietary component or food with no other change in the usual diet. In the case of fats, supplementation generally takes the form of oil, typically included in capsules, foods enriched in the specific fat, or foods new to the diet that are enriched in the fat. Research studies also employ all these ways of increasing intake, but blinding of subjects and researchers to treatments can be limited by the form of the supplement. For instance, neither subjects nor researchers can be blinded to the addition of fish to a diet, though researchers or technicians performing analyses can be blinded.

There are several studies showing DHA status at birth is related to maturation [Helland et al., 2001, 2003; Cheruku et al., 2002; Malcolm et al., 2003a; Bouwstra et al., 2006]. The majority of studies on fatty acid intake in pregnancy and lactation have focused on n–3 supplementation, with a few concerned specifically with AA. We consider each separately.

n–3 LCPUFA Supplementation

Quantitatively, the major n–3 PUFA found in tissue are ALA, EPA, docosapentaenoic acid (DPA) (n–3), and DHA. Minor amounts of 18:4n–3 (stearidonic acid, SDA) and 20:4n–3 (eicosatetraenoic acid) can also be found, as well as trace levels of the 24-carbon LCPUFA 24:5n–3 and 24:6n–3.

At least 19 studies in adults show that supplementation of ALA in the form of flaxseed, flax oil, or purified ALA results in increases in plasma, platelet, or RBC ALA, EPA, and DPA, but has no effect on DHA [Brenna, 2002; Plourde and Cunnane, 2007; Brenna et al., 2009]. Supplementation with 10 g/day of flax oil for 28 days similarly does not increase breast milk DHA [Francois et al., 2003]. Increases in blood DHA status ascribed to increasing dietary ALA intake involve changes in cooking oils that also reduce LA intake [Mantzioris et al., 1994, 1995; Ezaki et al., 1999; Ghafoorunissa et al., 2002], and thus reducing competition for incorporation into phospholipids, and possibly increasing conversion of ALA to DHA. Hypothetically, SDA was considered to be a more efficient precursor for LCPUFA because it is the product of ALA Δ6-desaturation, considered to be the rate-limiting step in LCPUFA biosynthesis because of the relatively low activity of this enzyme in vitro compared to the Δ5-desaturase [Su and Brenna, 1998]. The availability of SDA-enriched soy oil has shown SDA to be a more efficient precursor of EPA than ALA, but it does not increase human plasma DHA levels [James et al., 2003; Harris et al., 2008].

An increase in DHA status can be effectively achieved by increasing DHA intake by supplementation or increasing intake of foods containing DHA. Addition of either 57 g (2 oz) of sardines plus fish oil, providing about 1.1 g DHA per day starting at gestational weeks 24–30 and ending at week 34, showed significant increases in plasma and RBC DHA in mothers, and their infants showed a 45% increase in plasma DHA compared to controls [Connor et al., 1996]. Several other studies confirm that enhanced LCPUFA status, or nutrition, in fetal life or during lactation benefits the infant. Randomized placebo-controlled supplementation of pregnant women from week 30 of gestation with 2.7 g fish oil (32/23 EPA/DHA) increased DHA and EPA in umbilical plasma phospholipids, thus, showing that supplementation effectively improves fetal status [van Houwelingen et al., 1995]. Notably, AA decreased significantly in plasma, but was not significantly reduced in phospholipids of the vessel wall, which also showed a significant increase in DHA. An RCT of 400 mg DHA consumed from 15 weeks gestation to term resulted in 20% higher maternal blood DHA at 28 weeks and at term, and the maternal decrease in DHA during pregnancy was attenuated. No changes in cord blood DHA were found in this study [Montgomery et al., 2003]. A multicenter European RCT of 270 pregnant women administered 0.5 g DHA/0.15 g EPA from gestation week 22 to term produced an increase in

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maternal plasma DHA and EPA as well as significantly greater cord plasma DHA [Krauss-Etschmann et al., 2007].

It is clear, however, that supplemental ALA can increase blood concentrations of EPA and DPAn–3 in adults against a stable background diet, but not DHA. Changes in cooking oils that increase ALA and simultaneously decrease LA also show efficacy for increasing DHA, suggesting that lowering LA is key for increasing basal DHA levels attained from ALA. Recognizing that the main food n–3 is ALA, and that ALA does not serve as an efficient precursor of DHA outside the perinatal period, both ALA and DHA should be considered essential nutrients.

AA Supplementation

AA gives rise to a potent array of eicosanoids that modulate many physiological processes, playing signaling roles associated with coagulation and immune function. AA-derived prostaglandins are important for the maintenance of pregnancy and the initiation of labor [Khan et al., 2008], and it has long been known that urinary excretion of markers of prostaglandin synthesis are related to dietary AA intake in animals. AA and EPA/DHA are generally considered to be antagonistic in many bioactivities, and thus the study of supplemental AA in adults without co-administration of DHA or EPA + DHA, or in foods, is limited due to concern over possible deleterious effects on participants.

A small number of AA-alone supplementation trials involving a very limited number of adults have appeared. An early report of 6 g AA as ethyl ester orally administered to 4 adult men for 2–3 weeks showed greatly enhanced platelet aggregation and was stopped early for 2 of the participants, though no adverse symptoms were observed [Seyberth et al., 1975]. A trial of 1.5 g AA supplementation as triacylglycerol for 50 days was conducted in adult men [Ferretti et al., 1997; Kelley et al., 1997; Nelson et al., 1997a, b, c]. AA was markedly increased in plasma phospholipids and cholesteryl esters, and there was no change in platelet aggregation or in bleeding times and few changes in immune parameters, though urinary eicosanoids did increase [Kelley et al., 1997]. A study of 4 female and 4 male adults aged 56–70 years showed that moderate increase in AA of about 700 mg/day did not significantly influence pro-inflammatory cytokine production, plasma soluble adhesion molecules [Thies et al., 2001a], natural killer cells [Thies et al., 2001b], or T lymphocyte proliferation [Thies et al., 2001c]. The small number of non-pregnant, non-lactating adults who have participated in AA supplementation trials did not reveal any major adverse events, and some papers have noted this fact. An RCT of a combined dose of 0.26 g/day AA plus 0.57g/day DHA in pregnant women resulted in no change in RBC AA or total n–6 LCPUFA, though RBC DHA did rise [Otto et al., 2000]. Considering all available studies, there is no strong evidence in favor of an increase in AA apart from DHA for the health of pregnant women or their infants from supplementation trials.

Breast Milk LCPUFA

The fat content of breast milk is relatively constant at 3–4% by weight and delivers 50–60% of calories. The dominant LCPUFA in breast milk are DHA and AA, appearing at concentrations several-fold higher than the other LCPUFA. A comprehensive meta-analysis of breast milk composition reported means and SD of 0.32 ± 0.22% (range: 0.06–1.4%) for DHA and 0.47 ± 0.13% (range: 0.24–1.0%) for AA in 65 studies that included 2,474 women [Brenna et al., 2007]. DHA is more variable than AA on a relative basis (coefficient of variation: DHA = 69%, AA = 28%); breast milk DHA responds more sensitively to diet. A detailed study sampling about 50 women in 9 countries showed that the concentration of saturates and monounsaturates is also relatively constant, with substantial changes found only in the Philippines where lauric, myristic, and palmitic acids were elevated, consistent with high consumption of tropical oils. AA variability was among the least variable, ranging from 0.36 to 0.49%, while its precursor LA ranged from 7.9% in the Philippines to 17.8% in Chile. DHA ranged from 0.17% in North America to 0.99% in Japan, typically considered among the highest per capita fish consuming countries [Yuhas et al., 2006]. ALA had 5-fold relative range, from 0.43% in the Philippines to 2.0% in China. A study of breast milk in vegans, vegetarians, and omnivores showed significantly lower DHA in vegan milk (0.14 ± 0.06%, mean ± SEM; n = 19) compared to vegetarian (n = 5) or omnivore (n = 21) milks (0.30 ± 0.05% and 0.37 ± 0.07%, respectively), but no change in AA; 14-week-old breastfed infants of vegan mothers had less than a third the DHA concentration in erythrocyte lipids (1.9 ± 0.3%) than those of omnivore mothers (6.2 ± 0.4%), though AA concentrations were not different [Sanders and Reddy, 1992].

LCPUFA supplementation has long been known to influence breast milk PUFA concentrations [Jensen et al.,

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1992]. The influence of supplementation on breast milk DHA concentrations has been tested systematically. Fifty-two lactating women randomized to 5 supplement doses of DHA free of EPA in an algal oil showed dose-dependent increases in infant plasma phospholipids and RBC DHA, with no further increase in infant DHA status at breast milk DHA levels above 0.8% [Gibson et al., 1997]. About 1 g DHA/0.5 g EPA consumed from 1 week postpartum yielded breast milk with 1.16% DHA and 1.34% DHA at 2 and 4 months postpartum, respectively, compared to randomized controls with 0.3 and 0.4% at the 2 respective time points. The levels in supplemented women exceeded the levels of women in the 90th percentile of fish consumption in the same population, with average breast milk DHA of 0.60 and 0.74% at the 2 time points [Lauritzen et al., 2004]. An RCT of 200 mg DHA per day contained in a 200 ml drink increased breast milk DHA from 0.25 to 0.5% when consumed from 21 to 37 weeks' gestation and stopped at term [Bergmann et al., 2008]. Importantly, supplementation of lactating women with 10 g/day ALA from flaxseed oil for 28 days increased breast milk EPA and DPA, but not DHA [Francois et al., 2003].

A meta-analysis of 11 studies showed that breastfed infants have a cognitive advantage over formula-fed infants in the age range 6–23 months. These studies were conducted before the inclusion of LCPUFA in most infant formula, leading many to speculate that it is LCPUFA that are active components of breast milk [Anderson et al., 1999]. Studies of autopsy samples show that breastfed infants have higher cortex DHA compared to formula-fed infants [Farquharson et al., 1992; Makrides et al., 1994]. Tracer studies in the pregnant baboon, an omnivorous primate similar to humans, show that preformed DHA is about 20-fold more efficacious as a source of CNS DHA than the precursor ALA [Greiner et al., 1997]. Similar experiments show that the efficacy of DHA was 7-fold greater than ALA as a source of CNS DHA in baboon neonates [Su et al., 1999]. These data form strong evidence that preformed DHA is the specific component of breast milk than enhances CNS DHA in breastfed human infants rather than some combination of breast milk nutrients. Consistent with the human studies, a Japanese study comparing exclusive breast feeding versus formula feeding with up to 80% breast feeding in the first month of life found greater RBC DHA at 4 weeks of life and improved cognitive function in breastfed children at age 5 years as well as a correlation between cognitive function and 4-week RBC DHA levels [Tanaka et al., 2009].

Though the concentration of plasma phospholipid DHA and AA increases throughout pregnancy, the percent of fatty acids drops during pregnancy [Al et al., 1995], raising concerns about the adequacy of intake to support levels of bioactive structural lipids.

Estimates of Selected PUFA Intake by Pregnant Women

There are a limited number of studies directly reporting on the intake of fatty acids by pregnant women. Most highlight LCPUFA, and several recent studies focus on differences in intake and status in GDM. Table 1 lists 10 studies published between 1995 and 2006, and also includes NHANES III data for women of childbearing age for reference. Some reported on a comprehensive set of fatty acids, and others reported a subset of fatty acids. All data have been converted to means ± SD in units of mg/day for comparison, and 5 key PUFA are presented: LA, ALA, DHA, AA, and EPA. Seven of the 10 studies used recall questionnaire/interview methods (24-hour recall, FFQ) known to have high test-retest variability, while 2 others employed food records and 1 used duplicate diet analysis. Combining the 6 studies that did not consider GDM with the control groups from the GDM studies, the range of means for dietary intake in apparently normal pregnancy are: ALA, 989–1,600 mg/day, DHA, 38–300 mg/day, and AA, 20–198 mg/day. LA ranged from 7,888 to 14,795 mg/day, and EPA from 16 to 143 mg/day. No study accounted for the extremes of any PUFA. Only 1 developing country, Mexico, is represented, and it reported the greatest intake for AA [Parra et al., 2002]. The 1 study using duplicate diet analysis was within the ranges for ALA, DHA and AA, but had the low value for LA [Denomme et al., 2005]. NHANES III data on women of childbearing age (14–50 years, n = 6,340) are also within the range reported for pregnant and lactating women. In all cases, the SD calculated from the reported SEMs are larger than the means, highlighting both diversity of intake and high imprecision of dietary recall data. In addition, food composition tables used in NHANES III do not report LCPUFA levels with precision necessary for unbiased estimates.

GDM has been shown by several studies to result in altered blood fatty acid status, inspiring several studies of fat intake in GDM pregnancy. Four studies of GDM were identified, 2 reporting on women in Hartford, Conn., USA, and 2 in the UK. Three of 4 studies that compared normal pregnancy with GDM yielded differences in in-

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Table 1. PUFA intake (mg/day; mean ± SD) of pregnant women (or all women in NHANES III data)

	Location	Method	Subjects, n	LA	ALA	DHA	AA	EPA
Innis and Friesen, 2008	Canada	FFQ	135	13,500 ± 3,725	1,480 ± 475	110 ± 95	90 ± 25	70 ± 40
Denomme et al., 2005	Canada	Chemical analysis of 3-day duplicate food collections	20	7,998 ± 748	1,295 ± 161	82 ± 33	99 ± 19	35 ± 19
Innis and Elias, 2003	Vancouver	Food questionnaire	55	11,200 ± 2,966	1,600 ± 742	160 ± 148	121 ± 59	78 ± 15
Parra et al., 2002	Mexico City	FFQ	146	14,795 ± 8,920	1,518 ± 710	140 ± 110	170 ± 80	52 ± 40
De Vriese et al., 2001	Ghent	FFQ	26[a]	13,700 ± 5,900	1,500 ± 550	300 ± 190	130 ± 40	150 ± 90
Otto et al., 2001	Maastricht	FFQ	20	13,170 ± 4,025	1,090 ± 400	140 ± 220	20 ± 0	80 ± 134
Lewis et al., 1995	Nebraska USA	24-hour recall and 2-day food record	30	NR	989 ± 301	48 ± 81	NR	23 ± 60
NHANES III 1994–1996, 1998 (all women[b])	USA	Single 24-hour recall	6,340[d]	13,547 ± 16,293	1,210 ± 1,722	57 ± 366	NR	30 ± 203
Studies reporting intake in GDM								
Thomas et al., 2006	London	Food record (4 days)	Control, 44 GDM, 44	11,710 ± 5,180 12,210 ± 6,590	1,330 ± 560 1,420 ± 770	130 ± 140 200 ± 170[c]	120 ± 130 282 ± 174	110 ± 220 160 ± 250
Loosemore et al., 2004	Connecticut USA	24-hour recall	Control, 31 GDM, 14	11,560 ± 5,440 14,360 ± 6,560	1,340 ± 660 1,520 ± 880	68 ± 100 34 ± 19	155 ± 87 134 ± 70	16 ± 21 12 ± 9
Wijendran et al., 1999	Connecticut USA	24-hour recall (3 days)	Control, 15 GDM, 15	10,610 ± 3,880 11,720 ± 4,130	1,130 ± 310 1,300 ± 800	38 ± 33 87 ± 110[c]	106 ± 52 152 ± 50[c]	20 ± 21 51 ± 17[c]
Lakin et al., 1998	Aberdeen	FFQ	Omnivore, 7 Vegetarian, 4 Diabetic omnivore, 4	9,554 ± 2,751 10,446 ± 2,662 10,564 ± 3,524	1,218 ± 327 1,492 ± 202 1,405 ± 444	173 ± 51 9 ± 5[d] 270 ± 275	198 ± 51 42 ± 17[d] 289 ± 41[d]	143 ± 126 8 ± 5[d] 180 ± 186

NR = Not reported. All data converted to means ± SD. When the SEM was reported, SD was calculated by [SD = SEM × √n]; for Innis and Friesen [2008], error = (interquartile range)/2.

[a] Third trimester FFQ.

[b] Mean of reported intake for all females pooling ages 14–18, 19–30, 31–50 years; SD is calculated as the simple mean of SDs (source: www.ncbi.nlm.nih.gov/books/bv.fcgi?indexed=google&rid=hstat1a.section.38451).

[c] Significantly different from control.

[d] Significantly different from omnivore.

take of DHA or AA or both. Once diagnosed, GDM women are normally provided with dietary advice [Wijendran et al., 1999], which may explain why DHA and/or AA intake was higher in women with GDM.

The data confirm that LA intakes are on average more than 10-fold that of ALA. DHA and AA intakes are similar, and both are higher than EPA in most studies. They are not of sufficient precision or breadth to enable estimation of requirements for pregnancy and lactation.

Meta-Analyses and Systematic Reviews of LCPUFA Supplementation with Pregnancy Outcomes

Lengthening the gestational period to reduce preterm birth benefits both mother and fetus. A 2007 meta-analysis on the effects of LCPUFA supplementation in high-risk pregnancies on several parameters [Horvath et al., 2007] included 4 studies [Moodley and Norman, 1989; Bulstra-Ramakers et al., 1995; Onwude et al., 1995; Olsen et al., 2000], and on the basis of 2 [Bulstra-Ramakers et al., 1995; Olsen et al., 2000] concluded that LCPUFA supplementation reduced early preterm delivery (<34 weeks gestation; RR = 0.39, CI: 0.18–0.84), but found no significant effects for 12 other parameters. Another meta-analysis evaluated birth outcomes in 6 studies [Olsen et al., 1992; Helland et al., 2001; Malcolm et al., 2003b; Smuts et al., 2003a; Smuts et al., 2003b; Sanjurjo et al., 2004] and concluded that there is a mild increase of length of pregnancy with marine oil supplementation [Szajewska et al., 2006]. A 2006 Cochrane systematic review considered 6 trials [D'Almeida et al., 1992; Olsen et al., 1992, 2000; Bulstra-Ramakers et al., 1995; Onwude et al., 1995; Smuts et al., 2003b] of EPA or EPA + DHA on the risk of preeclampsia, preterm birth, low birthweight, and small-for-gestational age [Makrides et al., 2006]. An analysis of a subset of 3 trials [Olsen et al., 1992, 2000; Smuts et al., 2003b], deemed high quality, concluded that women allocated to a marine oil supple-

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ment had a mean gestational period 2.6 days longer than those allocated to placebo or untreated groups. The authors concluded that the evidence at that time was not sufficient to warrant routine use of marine oil to reduce the rate of preterm birth, low birthweight, small-for-gestational age, or preeclampsia. A reassessment of data from an RCT [Olsen et al., 2000] has appeared since this review showed lengthening of gestation in a group of 495 women with a history of preterm delivery, intrauterine growth restriction, or pregnancy-induced hypertension by supplementation with 2.7 g EPA + DHA from week 30 of gestation. An effect was detected in low and moderate fish eaters and no effect was detected in high fish eaters [Olsen et al., 2007]. The influence of habitual fish intake on gestational length and related measures may explain the mixed neutral and positive results on gestation length in previous studies.

Importantly, none of these studies reported substantial adverse effects of marine oil supplementation. Observation of benefit with a nutrient that poses negligible risk is strong evidence for recommending minimal consumption levels to optimize health on a population basis.

RCT with Infant Functional Outcomes

Numerous RCT on infant outcomes associated with n–3 LCPUFA supplementation in pregnancy and lactation have appeared. Table 2 shows 12 RCT that reported visual or cognitive outcomes in infants with administration of DHA or EPA or both in pregnancy, lactation or both. For the stated primary outcomes, 8 found positive effects upon original study conclusion or follow-up [Gibson et al., 1997; Helland et al., 2003; Jensen et al., 2005; Lauritzen et al., 2005a; Dunstan et al., 2008; Innis and Friesen, 2008; Krauss-Etschmann et al., 2008; Olsen et al., 2008]. Several showed positive effects in secondary analysis.

Evidence of DHA deficiency was reported, evaluated on the basis of below average visual acuity in infant girls of mothers receiving placebo rather than 400 mg/day DHA from week 16 of gestation to delivery [Innis and Friesen, 2008]. Problem solving and visual acuity was improved in infants of mothers receiving 214 mg/day DHA from week 24 of gestation to delivery [Judge et al., 2007a, b]. An RCT of a supplement delivering 200 mg DHA and 35 mg EPA from week 15 to term resulted in no change in visual evoked potential (VEP) and did not produce enhancement from supplement to placebo group. Coefficients of variation averaged >20%, and 18 or 24 infants were tested at 50 and 66 weeks post-conceptual ages. However, an association between infant DHA status at term and VEP was found at both time points, suggesting that enhanced prenatal DHA status is related to visual maturity [Malcolm et al., 2003b]. In another report from this study, infant electroretinography correlated with DHA status [Malcolm et al., 2003a], consistent with the findings for VEP.

A larger study randomized pregnant women to 10 g cod liver oil compared to corn oil controls. Increases in umbilical plasma phospholipid DHA, DPA (n–3), and EPA were found, but no significant difference was found for electroencephalograms (EEG) between the groups. However, at 2 days of life, neonates with mature EEG had greater DHA status, suggesting an advantage to those with enhanced DHA supply in utero [Helland et al., 2001]. A follow-up to this study involving about 20% of the original cohort found greater IQ of children at 4 years of age whose mothers were in the cod liver oil group, and the maternal intake of DHA was the only significant correlate of IQ at 4 years [Helland et al., 2001]. A follow-up at 7 years of age with a larger subset of the original cohorts did not find significant changes in IQ with the same test, but did reveal a significant correlation with maternal plasma phospholipid ALA and DHA during late pregnancy [Helland et al., 2008].

A supplementation study of 98 pregnant women reported numerous functional outcomes related to infant cognitive development [Dunstan et al., 2007, 2008] and to immune function [Dunstan et al., 2003a, b; Prescott et al., 2007]. Supplementation was with a fish-oil-derived mixture of 2.2 g DHA and 1.1 g EPA from midway through gestation to term. No negative effects were detected with this high-dose supplement [Dunstan et al., 2008]. Breast milk LCPUFA was greater than the olive oil control at day 3 postpartum (DHA: 1.15 vs. 0.5%; EPA: 0.16 vs. 0.06%), remained elevated at 6 weeks (DHA: 0.42 vs. 0.25%), and was back to baseline levels at 6 months. Cognitive assessment at 2.5 years of age correlated with day 3 and month 6 breast milk DHA levels [Dunstan et al., 2007]. Eye and hand coordination at 2.5 years was significantly greater in the fish oil group, and was correlated with cord blood DHA and EPA and inversely correlated with AA [Dunstan et al., 2008]. Stimulated production of leukotriene B4 [Prescott et al., 2007] and cytokines [Dunstan et al., 2003a, b] in cord blood neutrophils was lower in the fish oil group.

A supplementation trial with high levels of 1.2 g DHA/1.8 g EPA fish oil administered to 249 pregnant women in Bangladesh from week 25 of gestation to term showed no significant differences in the Bayley

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Table 2. RCT of n-3 LCPUFA in pregnancy and lactation that report functional outcomes other than birth outcomes (gestational length, birth weight, birth length)

Study	Participants[a]	Test dose	Dose	Duration	Primary functional outcome	Comments
Innis and Friesen, 2008	135	Algal oil	400 mg DHA	week 16 to delivery	Distribution of visual acuity suggestive of DHA deficiency in girls.	Visual acuity at 60 dpt (n.s.). Study was explicitly not designed to detect group differences.
Olsen et al., 2008	19 of 266	Fish oil	1.6 g EPA 1.1 g DHA or 4 g olive oil	week 30 to delivery	Reduced asthma and allergic asthma at 16 years.	Small subset of participants from Olsen et al., 1992.
Krauss-Etschmann et al., 2008	195	Fish oil	0.5 g DHA 0.15 g EPA	week 22 to delivery	Cord blood mRNA CCr4, IL-13, IL-4 lower and TGF-β higher.	
Judge et al., 2007b	29	Cereal-based bar with low EPA fish oil	0.214 g DHA	week 24 to delivery	Problem-solving improved in DHA group, age 9 months. Fagan test of infant intelligence (n.s.).	Participants overlap in these studies. Participants basal DHA intake averaged 80 mg/day.
Judge et al., 2007a	30	Cereal-based bar with low EPA fish oil	0.214 g DHA	week 24 to delivery	Visual acuity (Teller cards) improved at age 4 months; at age 6 months (n.s.).	
Tofail et al., 2006	249	Fish oil	1.2 g DHA; 1.8 g EPA or 2.3 g LA; 0.27 g ALA	week 25 to delivery	Bayley Mental Development Index and PDI, age 10 months (n.s.).	PDI 95% CI (–4.3 to 0.1) by multiple regression.
Jensen et al., 2005	~165	Algal oil	200 mg/day DHA	postpartum 5–120 day	Bayley PDI greater at 30 months. VEP amplitude lower at 4 and 8 months. Visual acuity (VEP, Teller cards) (n.s.). Several other neuro-developmental outcomes (n.s.).	
Lauritzen et al., 2004	97	Fish oil	1 g DHA 0.5 g EPA	postpartum 1 week to 4 months	Visual acuity (VEP) (n.s.).	Infant RBC DHA correlated with visual acuity at 4 months.
Lauritzen et al., 2005b	122	Fish oil	1 g DHA 0.5 g EPA	postpartum 1 week to 4 months	Problem solving at 9 months (n.s.). Passive vocabulary at 1 year (lower with fish than olive oil); at 2 years (n.s.).	Word comprehension at 1 year inversely correlated with 4-month RBC DHA.
Lauritzen et al., 2005a	72	Fish oil	1 g DHA 0.5 g EPA	postpartum 1 week to 4 months	Weight, height at 2.5 years (n.s.). BMI greater, head circumference greater at 2.5 years.	BMI correlated with maternal DHA at 4 months postpartum.
Lauritzen et al., 2005c	65	Fish oil	1 g DHA 0.5 g EPA	postpartum 1 week to 4 months	LPS-stimulated IFN-γ higher at 2.5 years.	No difference in IL-10 means; difference in IL-10 distribution.
Larnkjaer et al., 2006	66	Fish oil	1 g DHA 0.5 g EPA	postpartum 1 week to 4 months	Blood pressure, electrocardiogram pulse wave velocity, heart rate, heart rate variability at 2.5 years (n.s.).	–
Colombo et al., 2004	70	Eggs	133 mg DHA or 33 mg DHA	weeks 24–28 to delivery	Mental processing (look duration) improved with high DHA at ages 4 and 6 months; 8 months (n.s.). Increase in examining and less distractibility between age 1 and 2 years; attentional disengagement (n.s.).	Subset of participants in Smuts et al., 2003b.
Dunstan et al., 2003a	83 of 98	Fish oil	2.2 g DHA 1.1 g EPA	week 20 to delivery	Cord blood cytokine responses to cat allergen (n.s.); IL-10 response lower with fish oil.	–

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Table 2 (continued)

Study	Participants[a]	Test dose	Dose	Duration	Primary functional outcome	Comments
Dunstan et al., 2003b	83 of 98	Fish oil	2.2 g DHA 1.1 g EPA	week 20 to delivery	Cord blood IL-4, IL-5, IL-6, IL-12 (n.s.). IL-13 lower with fish oil.	Less severe disease at age 1 year.
Dunstan et al., 2007	~60	Fish oil	2.2 g DHA 1.1 g EPA	week 20 to delivery	Cognitive scores correlated with breast milk DHA and EPA at 2.5 years.	
Dunstan et al., 2008	72 of 98	Fish oil	2.2 g DHA 1.1 g EPA	week 20 to delivery	Eye-hand coordination favored fish at age 2.5 years.	Cord blood RBC DHA and EPA correlated with eye-hand coordination and inversely with AA.
Prescott et al., 2007	98	Fish oil	2.2 g DHA 1.1 g EPA	week 20 to delivery	Cord blood neutrophil LTB4, IL-6, IL-10 stimulated production lower with fish oil.	–
Malcolm et al., 2003a; Malcolm et al., 2003b	~25[b]/ group	Fish oil blend 40% DHA 7% EPA 4% DPA(n-6)	200 mg/day fish oil or sunflower oil	week 15 to delivery	Visual acuity (VEP, ERG) (n.s.).	Significant correlations found for VEP and ERG with infant DHA status.
Helland et al., 2001	341	Cod liver oil	10 g/day 1.18 g DHA 0.80 g EPA	week 18 of pregnancy to week 13 postpartum	EEG (n.s.). Fagan (n.s.).	Significant correlation of EEG with umbilical plasma phospholipid DHA.
Helland et al., 2003 (4-year)	84	Cod liver oil	10 g/day 1.18 g DHA 0.80 g EPA	week 18 of pregnancy to week 13 postpartum	IQ favoring cod liver oil at age 4 years.	Significant correlation of IQ with maternal DHA intake.
Helland et al., 2008 (7-year)	142	Cod liver oil	10 g/day 1.18 g DHA 0.80 g EPA	week 18 of pregnancy to week 13 postpartum	IQ (n.s.).	Significant correlation of IQ at age 7 with maternal phospholipid DHA and ALA in late pregnancy.
Gibson et al., 1997	52	Algal oil	0, 0.2, 0.4, 0.9, 1.3 g DHA	day 5 to week 12	Bayley MDI correlated with 12 weeks' breast milk, infant RBC, plasma DHA at age 1 year but not 2 years. Visual acuity (VEP) at 12 and 16 weeks (n.s.).	
Treatment for depression						
Su et al., 2008	24	Menhaden oil	1.2 g DHA 2.2 g EPA	mid-gestation, duration 8 weeks	Depressive symptoms reduced; higher response rate to treatment.	Strong responders to placebo ineligible for randomization to treatment.
Freeman et al., 2008	51	Fish oil	0.8 g DHA 1.1 g EPA	mid-gestation, duration 8 weeks	Depressive symptoms (n.s.).	
Rees et al., 2008	26	Fish oil	1.6 g DHA 0.4 g EPA	6-week total in trial (week 28 to 6 months postpartum)	Depressive symptoms (n.s.).	

n.s. = Not significant; MDI = Mental Development Index; PDI = Psychomotor Development Index; VEP = visual evoked potential; ERG = electroretinography.

[a] Total subjects of a group unless otherwise indicated.

[b] n varied based on outcome.

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Mental Development Index and Psychomotor Development Index scores at 10 months compared to a soybean oil dose (2.3 g LA, 0.27 g ALA) [Tofail et al., 2006]. However, the study statistics indicate the Psychomotor Development Index 95% CI as −4.3 to 0.1, which would have been considered marginally significant by some researchers.

One study found an apparently negative effect of fish oil delivering 1 g DHA and 0.5 g EPA to lactating mothers [Lauritzen et al., 2004]. This study used encapsulated fish oil baked into cookies as one form of supplementation when the original supply of supplement bars ran out; the negative effects may be due to oxidative products of fish oil at high heat.

A workshop of pediatric researchers in 2001 considered it premature to make recommendations for LCPUFA intake by pregnant and lactating women, though added that the weight of evidence suggested, at the time, that a prudent diet would have some DHA. An extensive 2005 AHRQ (Agency for Healthcare Research and quality) report on n–3 supplementation in child and maternal health was inconclusive about recommendations for intake [Lewin et al., 2005]. In 2007/2008, 2 independent workshops, led by B. Koletzko, included representatives from numerous professional organizations, some of which officially endorsed the workshop findings. The recommendation is for a minimum intake of 200 mg DHA per day for pregnant and lactating women, and a note was made that intakes up to 1 g/day DHA or 2.7 g/day LCPUFA (DHA + EPA) had been used in clinical trials without significant adverse effects [Koletzko et al., 2007, 2008]. Evidence considered in these recommendations includes most of the studies in table 2 along with prospective and retrospective studies and basic research results. They were based on the demands of the developing fetus/infant for DHA and the limited ability for biosynthesis of DHA from precursors.

Psychiatric Health in Pregnancy and Lactation

Effects of dietary n–3 LCPUFA on psychiatric disorders has received considerable attention recently. The human CNS is rich in DHA and, though EPA concentrations are low in the CNS, in some tissues, EPA competes with AA as a substrate for inflammation-mediating eicosanoids, including the newly described resolvins and related molecules. A range of other biochemical effects are also known, including those for the intermediate LCPUFA DPA. Depression is a major morbidity associated with pregnancy, and several studies showing associations of depression with reduced n–3 status have been published [Sontrop and Campbell, 2006]. A selective deficit in DHA has been reported in the postmortem orbitofrontal cortices of adults diagnosed with major depressive disorder, and the reduction was greater in females [McNamara et al., 2007]. Antidepressives may negatively influence the fetus [Moses-Kolko et al., 2005], while there is general agreement that preformed DHA and EPA have positive effects on the fetus and no evidence of adverse effects at nutritional or supranutritional levels.

LCPUFA and Depression in Men and in Non-Pregnant and Non-Lactating Women

A recent cross-sectional study of 21,800 residents of Norway showed a significant association between daily consumption of cod liver oil with lower incidence and severity of depression after adjustment for covariates [Raeder et al., 2007].

Numerous RCT and open-label trials testing dietary DHA, EPA, or both have shown either improvement or no changes in mood disorders with a near negligible incidence of side effects. A 2006 meta-analysis of 8 RCT [Stoll et al., 1999; Nemets et al., 2002; Peet and Horrobin, 2002; Marangell et al., 2003; Su et al., 2003; Silvers et al., 2005; Frangou et al., 2006; Keck et al., 2006] yielded a significant effect favoring n–3 treatment for unipolar and bipolar depression [Freeman et al., 2006b], leading to a recommendation by the American Psychiatric Association for all adults to eat fish at least twice weekly, and for patients with mood, impulse control, or psychotic disorders to consume at least 1 g EPA + DHA. A separate meta-analysis [Lin and Su, 2007] found a significant effect for 7 of these studies [Stoll et al., 1999; Nemets et al., 2002; Peet and Horrobin, 2002; Marangell et al., 2003; Su et al., 2003; Silvers et al., 2005; Frangou et al., 2006] as well as a subset that examined clearly defined depression [Nemets et al., 2002; Peet and Horrobin, 2002; Marangell et al., 2003; Su et al., 2003; Frangou et al., 2006]. Both meta-analyses found high heterogeneity and concluded that further study is necessary to understand specifics in which LCPUFA may be beneficial. A third meta-analysis found evidence of efficacy in major depression, but no evidence of efficacy in depressed mood [Appleton et al., 2006], similar to later RCT by the same authors who concluded that supplementation with 1.7 g DHA + EPA was not efficacious in correcting mild to moderate depression [Rogers et al., 2008]. The meta-analysis has been criticized for over-inclusiveness [Richardson, 2008].

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Trials appearing since then have similarly yielded results mixed between positive and no effects. A dose-response study of 35 adults (ages 42 ± 14 years) evaluated the efficacy of 1, 2, and 4 g/day DHA on improvement in depression, finding best efficacy for 1 g/day and significant but less improvement for 2 g/day; no improvement was found at the higher dose [Mischoulon et al., 2008]. Forty-nine adults of both genders and with a history of recurrent self-harm were randomized to supplements of mixed EPA + DHA (1.2/0.9 g) for 12 weeks and showed improvements in scores for depression, suicidality, and daily stresses [Hallahan et al., 2007]. An RCT of 83 adults of both genders found no differential improvement in depression between those that received tuna oil (2.2 g DHA and 0.6 g EPA) daily and an olive oil control. In this study, subjects had on average normal erythrocyte RBC levels upon entry and responded to standard antidepressive treatment, indicating that LCPUFA conferred no additional benefit. A crossover RCT of 1.6 g EPA/0.8 g DHA in 33 adults showed improvement in recent (5 day) mood state profile, which was enhanced for those on a high (55%) versus moderate (40%) carbohydrate diet [Fontani et al., 2005].

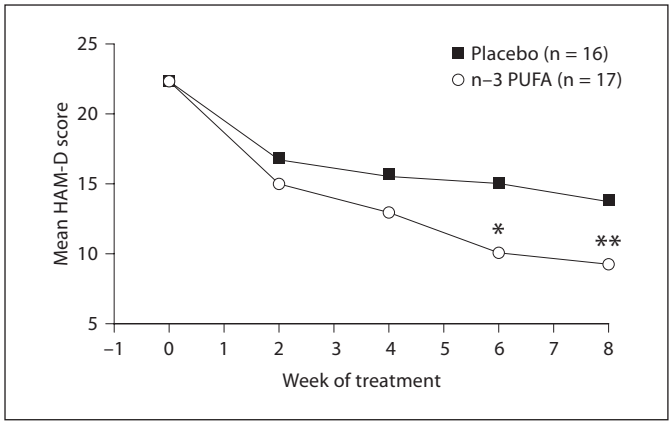

Fig. 1. Evolution of the 21-item Hamilton Rating Scale for Depression (HAM-D) scores in pregnant women with depression treated with n–3 PUFA or placebo during the study period (* p = 0.001, ** p = 0.019). All values represent the intention-to-treat population. Biweekly changes in the HAM-D scores illustrate a significantly greater decline in the n–3 group by mixed-model ANOVA. Adapted from Su et al. [2008].

LCPUFA, Psychiatric Health and Depression in Pregnant and Lactating Women

An ecological study showed a strong inverse relationship between the incidence of postpartum depression and apparent seafood consumption ($r = -0.81$, $p < 0.001$) on a countrywide basis [Hibbeln, 2002]. Lower phospholipids and cholesteryl ester DHA were decreased by 26 and 37%, respectively, in venous serum of women diagnosed with postpartum depression compared to controls, and DHA was the only PUFA that was significantly related to postpartum depression in this study [De Vriese et al., 2003].

Studies of depression treatment in the perinatal period are few, and several have been summarized in the lower section of table 2. One study of 36 depressed subjects, in which a menhaden oil concentrate delivering 1.2 g DHA and 2.2 g EPA reduced depression scores, showed positive results [Su et al., 2008]. In contrast to previous studies, a lead-in period of 1 week was used in which all subjects were provided with the placebo, and those with a 20% reduction in depression were excluded from the main study. Figure 1, taken from that study, shows a greater drop in depression score in the n–3 group compared to the placebo, reaching significance by week 6. Those in the n–3 group developed a significantly greater RBC DHA level than placebo (5.4 ± 1.5% vs. 4.6 ± 1.2%, $p < 0.03$). Other studies did not show significant improvements between n–3 PUFA and control, but also tended to have large placebo effects or variability in the outcome measures. Early small open-label studies [Marangell et al., 2004; Freeman et al., 2006a, c] showed no significant changes and no significant adverse reactions and all recommended further study. Fifty-six depressed pregnant and postpartum women receiving psychotherapy were randomized to 1.1 g EPA and 0.8 g DHA. No significant additional improvement was detected due to the LCPUFA treatment, though on average participants' depression improved and there was high variability in the outcome measures (coefficient of variation ~48%) [Freeman et al., 2008]. A study of 26 depressed women found no difference between those receiving 1.6 g DHA/0.4 g EPA in fish oil capsules for 6 weeks; however, the authors concluded that the study should not be considered definitive due to the small numbers and related experimental difficulties [Rees et al., 2008].

Two meta-analyses have appeared that evaluated studies of DHA/EPA in adult psychiatric health outcomes. Both [Freeman et al., 2006b; Lin and Su, 2007] considered the same set of studies on maternal psychiatric disorders and arrived at congruent conclusions, that there is a substantial positive effect. They also suggested that more research is necessary because of heterogeneity among studies. Based on these studies, the American Psychiatric Society has recommended an intake of DHA and EPA for psychiatric disorders.

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Genetic Polymorphism, Depression and Mental Health

Importantly, existing RCT treat DHA and EPA as therapeutics for the treatment of diagnosed depression. Unlike antidepressive drugs, DHA and EPA are nutrients that are normally present in all human diets apart from those of strict vegans. They are present at some non-zero level in all humans, and their augmentation as supplements may not be at doses appropriate to all individuals that are putative responders. That is, participants entering studies with higher DHA/EPA status may not benefit from supplementation because their depression is due to some cause unrelated to DHA/EPA, thereby reducing the statistical power of a study. Detailed genetic and molecular studies may reveal details necessary to distinguish responders from non-responders.

Some data are available to support alterations in PUFA status with specific genetic polymorphisms in the FADS1 and FADS2 genes, both required for PUFA biosynthesis in humans [Schaeffer et al., 2006] as well as for the putative fatty acid desaturase gene FADS3. Single nucleotide polymorphisms of the FADS1, FADS2, and FADS3 gene cluster (chromosome 11q12–13.1) have been associated with serum phospholipid levels of n–6 PUFA and ALA in a cohort of cardiovascular patients [Malerba et al., 2008]. RBC and plasma phospholipid AA and other n–6 levels are strongly related to genetic variants in FADS1 and FADS2 [Rzehak et al., 2009]. One study reported an association between IQ and FADS2 intronic SNP [Caspi et al., 2007], but, apart from this, no studies exist showing associations of PUFA-related genes and mental function. This is likely to be because large-scale genetic profiling is in its infancy and can be expected to be a topic of ongoing research.

Although most of these studies have treated DHA and EPA as therapeutics, evidence for their efficacy is also evidence for correction of a dietary deficiency condition. A recent large prospective study estimated DHA + EPA intake from seafood in 14,500 pregnant women and assessed maternal depression and infant neurodevelopment to 8 years. Seafood intake delivering 830 mg/day EPA + DHA was associated with protection against maternal depression, and 555–590 mg/day was associated with protection against suboptimal verbal IQ at age 8 years for 98% of the population, describing a putative recommended dietary allowance [Hibbeln and Davis, 2009]. These data were consistent with improved stereoacuity at 3.5 years for breastfed children of mothers who ate oily fish [Williams et al., 2001]. A prospective study of 25,000 children born to mothers in the Danish National Birth Cohort showed that higher maternal fish intake was independently associated with high child developmental scores at 18 months of age [Oken et al., 2008].

Considerations for Industrializing Countries

Rapid industrialization in developing countries has led to a major shift in the availability of high-quality seed oils that can be an important source of calories and are highly desired by consumers [Ghafoorunissa, 1996, 1998, 2005]. Many of these seed oils, such as sunflower, safflower, sesame, cottonseed, and groundnut (peanut) oils, are rich in LA, but ALA is either very low or absent. The consequences of wholesale substitution of all visible fats for those rich in LA and nearly devoid of ALA are not studied in human populations, but are well studied in animals. In rats [Benolken et al., 1973] and primates [Neuringer et al., 1986], deprivation of dietary n–3 PUFA is typically accomplished by use of sunflower [Bourre et al., 1989] or safflower [Salem et al., 2001] oils. Reproduction was apparently normal, as was growth. The absence of n–3 led to the expected very low concentration of DHA in all tissues, including retina and brain, and suboptimal development of the visual system and various functions of the CNS [Bourre et al., 1989]. Repletion studies, in which animals on an n–3 deficient diet are changed to a diet containing DHA, show that tissue composition recovers within a few weeks in most [Connor et al., 1990] but not all tissues [Anderson et al., 2005]. In spite of a >85% recovery of retina DHA, some functional parameters associated with the retinal response to light remain suboptimal into adulthood when deficiency occurs in utero [Anderson et al., 2005]. It is therefore important to ensure that ALA is included in cold use and cooking oils. The use of oils blended to yield a final composition with adequate ALA has been shown to improve n–3 status in India, as a convenient and straightforward example to avert the prospects of frank n–3 deficiency by overconsumption of ALA-deficient diets [Ghafoorunissa et al., 2002].

Recommendations for Intake

Total Fat

There is no evidence that the incremental dietary energy requirement in pregnancy and lactation should have a greater percentage of fat than in non-pregnant, non-lactating women. It is notable, however, that the caloric de-

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mands of pregnancy are difficult to meet with very-low-fat diets, as are requirements for PUFA.

Saturated, Monounsaturated, and Trans *Fats*

It is widely accepted that the saturated fatty acids (SFA) and MUFA in the human diet can be biosynthesized from acetate precursors, which include non-fat components (carbohydrates, glucogenic amino acids), and from PUFA. It has long been known that the proportion of specific SFA in the diet gives rise to specific metabolic effects. Distinct metabolic effects of the major dietary MUFA (oleic acid, *cis* 9–18:1; vaccenic acid, *cis* 11–18:1) have not been studied in humans.

Diets containing normal amounts of fat contain substantial amounts of SFA and MUFA. Low-fat human diets, those below 10% energy as fat, are encountered in the developed world in association with fad diets, and in the developing world as a result of high intake of low-fat grains, tubers, and pulses. Apart from energy malnutrition, there are no established negative effects specific to a putative deficiency of SFA or MUFA. There is no independent evidence for the incremental energy requirements in pregnancy and lactation for SFA or MUFA.

There exist sufficient data on TFA to warrant caution against consumption of foods with PHVO by women who are pregnant or lactating. Data in humans are largely associational, and do not permit setting a limit for safety during pregnancy and lactation and, therefore, PHVO intake should be as low as practical.

Long-Chain PUFA

DHA and EPA

As reviewed and noted in tables 1 and 2, there are numerous positive functional outcomes for the mother and infant with DHA and EPA intake. There is no basis for an independent effect of EPA in pregnancy and lactation since it has not been studied except when it was present with DHA as a component of a fish oil preparation. DHA has been studied alone and in combination with EPA, and there is some evidence that n–3 LCPUFA is more effective when EPA is present along with DHA for maternal depression. At least 2 studies providing DHA alone in pregnancy [Innis and Friesen, 2008] and lactation [Gibson et al., 1997] report cognitive or visual benefit to the infant at the few hundred mg/day range. We report on lactation first because the composition of breast milk and lactation-related studies enable direct estimates of utilization.

Lactation. Through the first 6 months of life, exclusively breastfed infants consume an average of 836 ± 143 g of breast milk per day with a fat content of 41.1 ± 7.8 g/l [Kent et al., 2006]. The global average DHA content of human breast milk is 0.32 ± 0.22% [Brenna et al., 2007]; thus, the average breast milk DHA output can be calculated to be 110 mg/day. This figure can be compared to a study from western Australia reporting breast milk DHA output of about 49 mg/day for women, with mean breast milk DHA of 0.19%, well below the global mean [Mitoulas et al., 2003]. A simple proportionality [(0.32/0.19) × 49] indicates that an increase in breast milk DHA concentration in these women would put their daily output at 82 mg/day, closer to the calculated global mean. We consider the global mean because it is representative of a broad array of populations.

Blood and breast milk DHA status are not improved by consumption of precursors, and isotopic tracer studies are consistent with these studies, showing very low conversion rates [Pawlosky et al., 2006]. Assuming that DHA biosynthesis is negligible compared to output, 110 mg/day may be taken as a mean minimal replacement nutrient intake not allowing for any inefficiency of transfer to milk or use elsewhere by the lactating woman. A dose-response study reported on the range of breast milk DHA with DHA supplementation from 0 to 1.3 g/day [Gibson et al., 1997]. The group receiving no DHA supplement had breast milk DHA = 0.21%, low compared to the global mean, showing that the basal diet of this population is low in DHA. This value is also close to that of vegetarian mothers. A regression analysis of the data presented in figure 2 shows a very high correlation between intake and breast milk DHA. Using the equation of that line, breast milk DHA at the global mean of 0.32% requires DHA intake of 167 mg/day above basal intake. The global mean +2 SD would correspond to a breast milk level of 0.76%, providing 261 mg/day DHA to the infant, which requires DHA intake of 778 mg/day. Finally, breast milk DHA at the 98th percentile globally is estimated to be about 1% [Brenna et al., 2007]; this level would require maternal DHA intake of 1,111 g/day. Notably, the dose-response study showed that infant blood DHA reached a plateau when breast milk DHA delivered about 800 mg/day [Gibson et al., 1997]. These values are summarized in table 3.

Based on these considerations, an average nutrient requirement for DHA in lactation can be set at 200 mg/day, rounded for eased of reference. Meeting an INL_{98} (individual nutrient level) at the +2 SD (+780 mg/day) or 98% DHA composition level (+1,100 mg/day) based on foods would require very judicious selection of fatty fish rich in DHA, considering compositions discussed in 'Implications for Food-Based Dietary Guidelines'. There is, at this

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Table 3. Calculation of mean DHA output via breast milk and corresponding dietary intake, in the first 6 months postpartum

	Amount	Reference
Breast milk consumed by infant, g/day	836 ± 143	Kent et al., 2006
Breast milk fat content, g/l	41.1 ± 7.8	Kent et al., 2006
Global mean breast milk DHA		
Output	0.32 ± 0.22% 110 mg/day	Brenna et al., 2007
Output + 2 SD	0.76% 261 mg/day	Brenna et al., 2007
Output <98%	1% 344 mg/day	Brenna et al., 2007
To achieve breast milk DHA of	Incremental maternal DHA intake, mg/day	
0.32%	167	
0.76%	778	
1%	1,111	

Maternal DHA intake (I) vs. breastmilk DHA (B):
B = (0.72 × I) + 0.20, using data of Gibson et al. [1997].

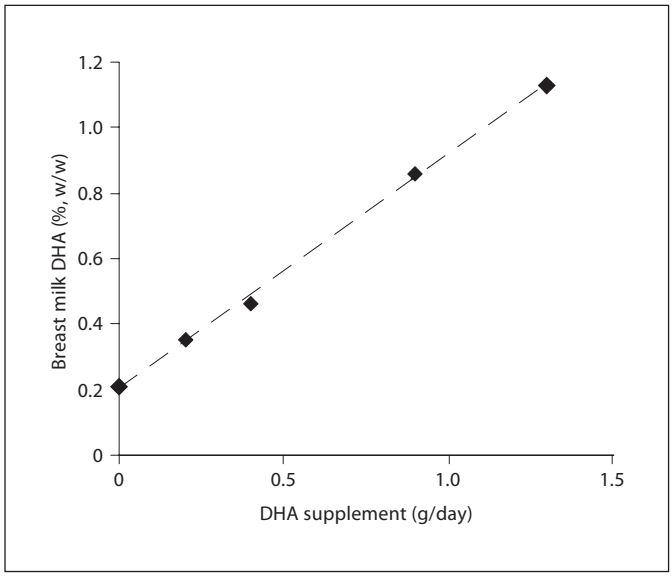

Fig. 2. Regression analysis of breast milk DHA (B) concentration vs. DHA intake (I). B = (0.72 × I) + 0.20 (r^2 = 0.998). Data from Gibson et al. [1997].

Table 4. Recommended nutrient intake values in pregnancy and lactation

	Average nutrient requirement	Upper nutrient limits
DHA	200 mg/day	1.0 g/day[a]
DHA + EPA	300 mg/day[b]	2.7 g/day[a]
AA		800 mg/day[a]
Industrial *trans* fatty acids		as low as practical

[a] No observed adverse effect level in RCT.
[b] Based on minimum adult average nutrient requirement plus an increment for energy demands of pregnancy.

writing, insufficient evidence based on functional outcomes to justify recommendations at these higher levels in normal populations. An average nutrient requirement for DHA is recorded in table 4.

Pregnancy. The majority of DHA dedicated to the conceptus is carried by the newborn, which emerges with total body DHA accretion averaging 14 mg/day through gestation (3,800 mg DHA/280 days of gestation). The placenta averages 450 ± 90 g [Molteni, 1984] and has 5.4 ± 0.3 mg/g fatty acids, of which 5.3 ± 0.2% is DHA [Larqué et al., 2003]; thus, loss of DHA with the placenta is minor on a per day-of-pregnancy basis, about 130 mg or <1 mg/day, for the course of gestation. DHA intake required to replace DHA carried away by the conceptus at parturition is therefore about 15 mg/day, a value that is small compared to daily intake for all but vegans, as shown in table 1. DHA intake of pregnant women ranges from 34 to 300 mg/day in omnivores, and 9 mg/day in vegans. The 1 study that analyzed duplicate diets showed a low mean intake, and the others, all based on recall methods and use of nutrient tables, are suspect because of concerns with biases in both methods. Breast milk DHA levels are an accurate biomarker for intake of lactating women. Assuming that women's diets do not change radically between pregnancy and lactation, DHA intake is probably best estimated by breast milk DHA levels, as shown in the preceding section.

Studies reporting benefit to the infant use DHA doses as low as 133 mg/day [Colombo et al., 2004] and reduce signs of DHA deficiency at 400 mg/day [Innis and Friesen, 2008]. Higher levels may be necessary to show therapeutic benefit for conditions induced by multiple causes as well as evaluations which employ less-sensitive outcome measures that are subject to strong placebo effects. Studies of treatment of depression suggest that doses of 1 g EPA + DHA or more are efficacious, as discussed in 'Psychiatric Health in Pregnancy and Lactation'.

Recent estimates of DHA + EPA intake efficacious toward reduction in maternal depression and risk for sub-

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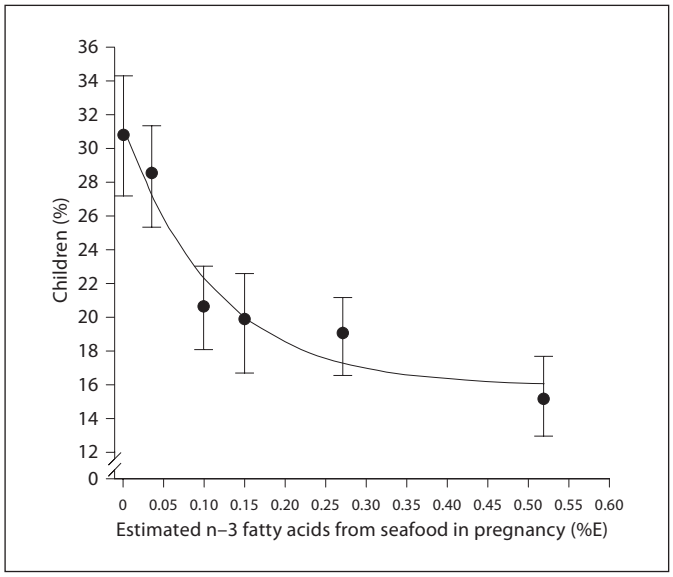

Fig. 3. Dose-response for prevalence of children in the lowest quartile for verbal IQ aged 8 years based on maternal seafood consumption during pregnancy. At seafood consumption corresponding to LCPUFA intake of 0.10%E (about 300 mg/day), the reduction in risk for low verbal IQ drops from 31 (no seafood consumption) to about 20.5%. With 5 times more seafood consumption, the risk drops to about 15.5%. Adapted from Hibbeln et al. [2007b].

optimal IQ were 389 and 114 mg/day, respectively, leading to an estimate of 830 mg/day EPA + DHA from seafood to meet nutritional requirements for 98% of a large population [Hibbeln and Davis, 2009]. Rounding the 389 mg/day for maternal depression to 400 mg/day, and recognizing that the relative proportion of DHA and EPA in seafood is approximately comparable, DHA intake is about 200 mg/day. Because ALA serves as an effective precursor for EPA, as measured in blood [Brenna et al., 2009], the independent evidence for EPA intake apart from ALA is less compelling than for DHA.

These latter data are, however, based on seafood consumption and not on LCPUFA specifically [Hibbeln et al., 2007a]; thus, the totality of effects cannot strictly be ascribed to EPA and DHA. Figure 3 [Hibbeln et al., 2007b] shows the dose-response of verbal IQ at age 8 years to the maternal seafood consumption in pregnancy. Intakes were divided into quintiles and compared to those reporting no seafood consumption. Risk of being in the lowest quartile of IQ was greatest for 8 year olds whose mothers consumed no seafood during pregnancy. The curve drops more steeply at low consumption and shows that most of the benefit is derived by the second quintile of seafood consumption, where mean LCPUFA intake is 0.1%E, corresponding to about 300 mg/day LCPUFA on a 2,500 cal/day diet.

In pregnancy, DHA demand will be greatest in the third trimester. Establishing requirements on a trimester basis should be avoided for at least 2 reasons. Unlike many water soluble nutrients, fat is stored in adipose and elsewhere, and can be mobilized when there is metabolic need. Establishing separate requirements on a trimester basis is bound to be confusing to women and unworkable for food suppliers serving pregnant women. However, it should be emphasized that much of the benefit from dietary fat can be derived if recommended levels are consumed after pregnancy is established, unlike nutrients that are active in critical processes in the first days after conception.

The WHO minimum acceptable macronutrient distribution range for men and non-pregnant/non-lactating women is set at 250 mg/day EPA + DHA, based on benefit for prevention of cardiovascular disease. Although food sources of LCPUFA will, on average, provide similar amounts of EPA and DHA, strict interpretation of the acceptable macronutrient distribution range allows for DHA to range between 0 and 250 mg/day. Women seeking to follow this guideline and allow an increment for additional energy demands of reproduction may consider an average increment of 300 cal/day in pregnancy, and 500 cal/day in lactation. Total energy requirements in pregnancy and lactation are then 2,300 and 2,500 cal/day, respectively, which correspond to increments of 115 and 125% above the non-pregnant and non-lactating levels. These lead to total recommended EPA + DHA intakes of 288–313 mg/day. Rounding for ease of reference leads to the recommendation of an intake of at least 300 mg/day EPA + DHA, of which 200 mg/day are DHA.

Upper Nutrient Limits. Recent studies in humans have failed to establish negative effects of very high DHA and EPA intake. Notably, infants with insufficient intestinal length or function to absorb enteral nutrients were fed parentally on conventional soybean or soybean/safflower oil emulsions and developed cholestasis. At 14 weeks of life they were switched to a highly refined fish oil preparation and compared with those who continued to be fed parenterally on soybean emulsions. The fish oil emulsion contained DHA (1.4–3.1 g/100 ml), EPA (1.3–2.8), and AA (0.1–0.4) as the sole source of fat compared to soybean or soybean/safflower emulsions containing no n–3 LCPUFA. Cholestasis was reversed rapidly (9 vs. 44 weeks), and fish oil was not associated with negative effects com-

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pared to the prior period and enhanced growth [Gura et al., 2008], consistent with a previous case report of 2 similar infants [Gura et al., 2006]. Parenteral nutrition with fish oil has been ongoing over periods of up to 4 years in children that are closely monitored on a clinical outpatient basis, and it supports normal growth and cognitive development [Puder, 2008]. These studies of very high chronic consumption of refined DHA and EPA, showing rapid recovery of critically ill infants and sustained normal or even accelerated development, suggest a high degree of safety and efficacy of DHA and EPA themselves. RCT of levels up to 1 g/day DHA and 2.7 g/day n–3 LCPUFA have shown no significant adverse effects [Koletzko et al., 2007, 2008]. These levels can be taken as the upper nutrient limits, defined as 'no observable adverse effect levels', with strong evidence that levels many fold higher are also safe. These refer only to n–3 LCPUFA and not to n–6 LCPUFA, especially AA.

Arachidonic Acid

Unlike DHA and EPA in marine foods, there is no particularly rich dietary source of AA. A few fish, including farmed fish fed corn and some tropical fish used for human food [Sinclair et al., 1983], do contain high amounts of AA [Weaver et al., 2008], but AA is generally not highly concentrated in any one food group. Data on effects of prenatal AA consumption in humans are scant, and research is mostly limited to several animal studies. A 2008 review [Hadders-Algra, 2008b] suggested that AA consumption in pregnancy should provide a balance between DHA and AA primarily on the basis of animal studies; however, this view has been challenged [Hadders-Algra, 2008a; Koletzko, 2008]. Studies in pregnant rats show poorer auditory and motor development in pups with low tissue AA as a result of high maternal DHA consumption. However, these studies employ levels of DHA that are either unlikely to be achieved by diet or unrealistic for humans (35% [Wainwright et al., 1997], 22% menhaden oil [Saste et al., 1998], 3% of energy as DHA [Haubner et al., 2002], 10% by weight unspecified fish oil as exclusive source of fat [Amusquivar et al., 2000]). The studies may suggest a functional neurological role for AA for which DHA cannot substitute. However, DHA and EPA in rodent studies are typically added to feed, and the highly oxidizable nature of DHA and EPA could result in the generation of small amounts of potently bioactive oxygenated compounds.

There are a very limited number of studies on AA nutrition in adult humans. There are no studies in pregnant women that specifically show benefit to dietary levels of AA apart from DHA and EPA. A combination of AA and DHA action improved mental development in formula-fed infants, while there was no change with DHA alone [Birch et al., 2000]. Numerous studies show that plasma and RBC AA drop with DHA and EPA supplementation [e.g. Conquer and Holub, 1996]. Whether these decreases are of importance has not been established. AA levels are conserved to a greater degree than DHA levels, thought to be at least in part due to the 3 enzymatic steps required for AA synthesis from LA compared to 7 steps in the accepted pathway for DHA from ALA; competition for incorporation into membrane phospholipids is also a factor that can reduce AA levels. Studies in neonatal baboons show that AA in formula does not increase brain AA when DHA is present in comparable amounts, though DHA does increase with dietary DHA level [Sarkadi-Nagy et al., 2003; Diau et al., 2005], indicating AA levels are more tightly regulated than DHA. An RCT of healthy non-pregnant non-lactating reproductive-age women showed that co-administration of DHA with the AA precursor γ-linolenic acid raised DHA levels while maintaining AA status [Geppert et al., 2008]. Direct AA supplementation is likely to be effective; however, administration of AA without a balance of EPA and/or DHA raises concerns because AA is a precursor of eicosanoids with potent bioactivities.

There is, at present, no basis for an independent requirement for AA in pregnancy and lactation. There is also no evidence base for an upper nutrient limit in pregnancy or lactation since it has not been studied as a pure component in pregnancy. A prudent recommendation is that intakes should not exceed normal dietary levels; that is, intake of AA through dietary supplements should not be at pharmacological levels. Table 1 shows that the highest reported AA intake is 282 ± 174 mg/day (mean ± SD) for GDM mothers in London. An upper nutrient limit consisting of this value plus 3 SD (800 mg/day) is a reasonable compromise as a 'no observable adverse effect level'.

LA and ALA

LA exerts its effects as a precursor to AA and may have other effects as well. In part because of the high intake of LA worldwide, there are no studies of hypothetical deficiencies of LA in humans. There is no support for an enhanced intake of LA in pregnancy and lactation.

Similar to LA, ALA is thought to exert its metabolic influence as a precursor to n–3 LCPUFA. ALA intake supports and enhances EPA and DPA statuses, but not DHA status as measured by blood biomarkers [Brenna et al.,

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2009]. The majority of research in humans and animals indicates that the high LA intake characteristic of modern dietary fat based on seed oils reduces the conversion of ALA into LCPUFA and LCPUFA incorporation into membranes. Studies of enhanced ALA typically show no increase in DHA, and studies with functional outcomes have focused on DHA or DHA + EPA supplementation. There is therefore no evidence for an independent effect of an increment of ALA in pregnancy and lactation.

No recommendation can be made for an incremental increase in ALA and LA apart from maintenance of their dietary levels as a percent of energy.

Implications for Food-Based Dietary Guidelines

The 3 dietary essential fatty acids are LA, ALA, and DHA. No LCPUFA, including DHA, is produced naturally in terrestrial plants, though they are produced abundantly by single-cell marine organisms.

LA is easily obtained in adequate quantities from almost all vegetable oils. Soybean, safflower, sunflower, groundnut (peanut), maize (corn), palm, canola, and olive oils from warmer climates are all good sources. Fewer oils are good sources of ALA, notably flax, perilla, and canola oils, with normal soybean oil delivering modest amounts of ALA. Both LA and ALA requirements can be met by these oils.

DHA is normally obtained in hundreds of milligrams by consumption of fish, and most bodies recommending DHA or DHA + EPA consumption recommend consumption of 2 oily fish meals per week, regardless of their recommendation of mg/day values for these LCPUFA.

Compilations of fish LCPUFA composition often add DHA and EPA to yield a single category. However, the proportions of DHA and EPA vary dramatically from fish to fish and among supplements, with algal supplements containing exclusively DHA, and many fish and supplement preparations dominated by EPA.

Estimated seafood disappearances in the USA in 2004 were presented in a 2007 report of the Institute of Medicine, and are given in table 5 in order of disappearance in the USA [Nesheim and Yaktine, 2007]. The amount and proportion of DHA and EPA varies substantially, with DHA ranging from 38 to 1,457 and EPA from 4 to 1,010 mg per 100 grams of cooked fish. Similarly, the ratio DHA/EPA varies from 0.3 to 39 depending on species; even within a particular type of fish, such as salmon, the dominant LCPUFA is inconsistent. Content of related LCPUFA also tend to be ignored. Notably, warm water fish such as tilapia have substantial amounts of AA, though consumption of these fish has not caused concerns over high AA intake in at least one small short-term study [Sinclair and Mann, 1996]. Most groups recommending fish consumption suggest at least 2 meals of fatty fish per week, despite several-fold variations in the recommended amount of daily LCPUFA intake. The worldwide harvest of fish to satisfy this need may not be sufficient unless fish production involving fish husbandry and ocean farming increases supply.

Concern over contamination of seafood continues to receive attention because of possible influences on the developing fetus. The main contaminant of concern is methyl mercury, a neurotoxic compound found in seafood, and particularly in large species occupying high trophic levels (high on the food chain). Shark, swordfish, tilefish, and albacore tuna have all been cited as containing levels of methyl mercury that may cause concern, though no detrimental effects have been detected from fish consumption per se, apart from frank poisoning events. Of these, albacore tuna is the most commonly

Table 5. Mean amount of DHA and EPA (mg) per 100 g of cooked fish, in rank order of consumption in the USA [Nesheim and Yaktine, 2007]

Rank[1]	Fish species	DHA[2]	EPA	DHA/EPA	DHA %[3]
1	Shrimp	144	171	0.8	46
2	Canned light tuna[4]	223	47	4.7	83
2	Canned white tuna[4]	629	233	2.7	73
3	Atlantic salmon[5]	1,457	690	2.1	68
3	Chinook salmon	727	1,010	0.7	42
4	Pollock	451	91	5.0	83
5	Catfish	128	49	2.6	72
6	Tilapia[6]	130	60	2.2	68
7	Crab[7]	38	124	0.3	23
8	Atlantic cod	154	4	39	97
9	Clams	146	138	1.1	51
10	Flatfish[8]	258	243	1.1	51

[1] Rank (highest to lowest) of seafood disappearing from the American economy, 2004. Tuna and salmon species were unspecified; thus, 2 entries from the USDA nutrient database are provided.

[2] www.health.gov/dietaryguidelines/dga2005/report/html/table_g2_adda2.htm.

[3] Of the total of EPA + DHA.

[4] Light = mixed species; white = albacore.

[5] Farmed.

[6] USDA Nutrient Database: www.ars.usda.gov/Services/docs.htm?docid=5720.

[7] Farmed, mixed species.

[8] Flounder and sole.

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consumed, and notably, it also has significant quantities of DHA. Full consideration of the issue surrounding seafood contamination is well beyond the scope of this report, and interested readers are referred to reports and ongoing evaluation efforts by government and other agencies [e.g. Nesheim and Yaktine, 2007].

Other animal foods contain LCPUFA and can be enriched with LCPUFA. LCPUFA-enriched eggs can be produced from chickens fed either ALA or, more efficiently, DHA + EPA. Ruminant meat (beef and mutton) has some DHA, but resists enrichment because rumen organisms secrete enzymes that isomerize and saturate PUFA. However, the feeding regime of cattle makes meat richer in LCPUFA [Ponnampalam et al., 2006], and small increases in beef LCPUFA content can add significantly to dietary DHA intake in developed countries because of high beef consumption.

Commercial efforts are underway to produce transgenic plants that include LCPUFA. Soybean oil that includes the ALA product SDA (18:4n–3) has been tested in humans and shown to be a more efficient precursor of EPA and DPA than ALA. Transgenic plants that yield oils with LCPUFA are potentially a food-based LCPUFA source compatible with strict vegan diets, and would represent a sustainable long-term solution to the harvest of DHA from fish.

Disclosure Statement

Dr. Brenna has served as a consultant for Mead Johnson Nutrition, Martek Biosciences, and the National Healthy Mothers, Healthy Babies Coalition. He has been a Principal Investigator for a DHA nutrition study funded by Mead Johnson Nutrition resulting in pending patent applications relating to dietary DHA levels. Dr. Lapillonne is currently serving as a consultant for Mead Johnson Nutrition. He has provided (2008) scientific recommendations for the World Association of Perinatal Medicine Dietary Guidelines Working Group, which was partially supported by Martek Biosciences Corp. USA.

References

Aitchison JM, Dunkley WL, Canolty NL, Smith LM: Influence of diet on *trans* fatty acids in human milk. Am J Clin Nutr 1977;30:2006–2015.

Al MD, van Houwelingen AC, Hornstra G: Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcome. Am J Clin Nutr 2000;71(1 suppl):285S–291S.

Al MD, van Houwelingen AC, Kester AD, Hasaart TH, de Jong AE, Hornstra G: Maternal essential fatty acid patterns during normal pregnancy and their relationship to the neonatal essential fatty acid status. Br J Nutr 1995;74:55–68.

Albuquerque KT, Sardinha FL, Telles MM, Watanabe RL, Nascimento CM, Tavares do Carmo MG, Ribeiro EB: Intake of *trans* fatty acid-rich hydrogenated fat during pregnancy and lactation inhibits the hypophagic effect of central insulin in the adult offspring. Nutrition 2006;22:820–829.

Amusquivar E, Rupérez FJ, Barbas C, Herrera E: Low arachidonic acid rather than alpha-tocopherol is responsible for the delayed postnatal development in offspring of rats fed fish oil instead of olive oil during pregnancy and lactation. J Nutr 2000;130:2855–2865.

Anderson GJ, Neuringer M, Lin DS, Connor WE: Can prenatal n–3 fatty acid deficiency be completely reversed after birth? Effects on retinal and brain biochemistry and visual function in rhesus monkeys. Pediatr Res 2005;58:865–872.

Anderson JW, Johnstone BM, Remley DT: Breast-feeding and cognitive development: a meta-analysis. Am J Clin Nutr 1999;70:525–535.

Appleton KM, Hayward RC, Gunnell D, Peters TJ, Rogers PJ, Kessler D, Ness AR: Effects of n–3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. Am J Clin Nutr 2006;84:1308–1316.

Arbuckle LD, Innis SM: Docosahexaenoic acid is transferred through maternal diet to milk and to tissues of natural milk-fed piglets. J Nutr 1993;123:1668–1675.

Barker DJ: The origins of the developmental origins theory. J Intern Med 2007;261:412–417.

Bazinet RP, Douglas H, Cunnane SC: Whole-body utilization of n–3 PUFA in n–6 PUFA-deficient rats. Lipids 2003;38:187–189.

Benolken RM, Anderson RE, Wheeler TG: Membrane fatty acids associated with the electrical response in visual excitation. Science 1973;182:1253–1254.

Bergmann RL, Haschke-Becher E, Klassen-Wigger P, Bergmann KE, Richter R, Dudenhausen JW, Grathwohl D, Haschke F: Supplementation with 200 mg/day docosahexaenoic acid from mid-pregnancy through lactation improves the docosahexaenoic acid status of mothers with a habitually low fish intake and of their infants. Ann Nutr Metab 2008;52:157–166.

Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG: A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. Dev Med Child Neurol 2000;42:174–181.

Bitsanis D, Crawford MA, Moodley T, Holmsen H, Ghebremeskel K, Djahanbakhch O: Arachidonic acid predominates in the membrane phosphoglycerides of the early and term human placenta. J Nutr 2005;135:2566–2571.

Bo S, Menato G, Lezo A, Signorile A, Bardelli C, De Michieli F, Massobrio M, Pagano G: Dietary fat and gestational hyperglycaemia. Diabetologia 2001;44:972–978.

Borgman RF, Bursey RG, Caffrey BC: Influence of maternal dietary fat upon rat pups. Am J Vet Res 1975;36:799–805.

Bourre JM, Francois M, Youyou A, Dumont O, Piciotti M, Pascal G, Durand G: The effects of dietary alpha-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. J Nutr 1989;119:1880–1892.

Bouwstra H, Dijck-Brouwer J, Decsi T, Boehm G, Boersma ER, Muskiet FA, Hadders-Algra M: Neurologic condition of healthy term infants at 18 months: positive association with venous umbilical DHA status and negative association with umbilical *trans*-fatty acids. Pediatr Res 2006;60:334–339.

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Brenna JT: Efficiency of conversion of alpha-linolenic acid to long chain n–3 fatty acids in man. Curr Opin Clin Nutr Metab Care 2002; 5:127–132.
Brenna JT, Salem N Jr, Sinclair AJ, Cunnane SC; International Society for the Study of Fatty Acids and Lipids: α-Linolenic acid supplementation and conversion to n–3 long chain polyunsaturated fatty acids in humans. Prostaglandins Leukot Essent Fatty Acids 2009;80:85–91.
Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM: Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr 2007;85:1457–1464.
Bulstra-Ramakers MT, Huisjes HJ, Visser GH: The effects of 3 g eicosapentaenoic acid daily on recurrence of intrauterine growth retardation and pregnancy induced hypertension. Br J Obstet Gynaecol 1995;102:123–126.
Burdge GC, Calder PC: Conversion of alpha-linolenic acid to longer-chain polyunsaturated fatty acids in human adults. Reprod Nutr Dev 2005;45:581–597.
Carnielli VP, Simonato M, Verlato G, Luijendijk I, De Curtis M, Sauer PJ, Cogo PE: Synthesis of long-chain polyunsaturated fatty acids in preterm newborns fed formula with long-chain polyunsaturated fatty acids. Am J Clin Nutr 2007;86:1323–1330.
Caspi A, Williams B, Kim-Cohen J, Craig IW, Milne BJ, Poulton R, Schalkwyk LC, Taylor A, Werts H, Moffitt TE: Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. Proc Natl Acad Sci USA 2007;104:18860–18865.
Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC: Dietary fatty acid intakes and the risk of ovulatory infertility. Am J Clin Nutr 2007;85:231–237.
Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ: Higher maternal plasma docosahexaenoic acid during pregnancy is associated with more mature neonatal sleep-state patterning. Am J Clin Nutr 2002;76:608–613.
Clandinin MT, Chappell, Heim T, Swyer PR, Chance GW: Fatty acid utilization in perinatal de novo synthesis of tissues. Early Hum Dev 1981;5:355–366.
Clark KJ, Makrides M, Neumann MA, Gibson RA: Determination of the optimal ratio of linoleic acid to alpha-linolenic acid in infant formulas. J Pediatr 1992;120(part 2):S151–S158.
Colombo J, Kannass KN, Shaddy DJ, Kundurthi S, Maikranz JM, Anderson CJ, Blaga OM, Carlson SE: Maternal DHA and the development of attention in infancy and toddlerhood. Child Dev 2004;75:1254–1267.
Connor WE, Lowensohn R, Hatcher L: Increased docosahexaenoic acid levels in human newborn infants by administration of sardines and fish oil during pregnancy. Lipids 1996; 31(suppl):S183–S187.
Connor WE, Neuringer M, Lin DS: Dietary effects on brain fatty acid composition: the reversibility of n–3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. J Lipid Res 1990;31:237–247.
Conquer JA, Holub BJ: Supplementation with an algae source of docosahexaenoic acid increases (n–3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. J Nutr 1996;126:3032–3039.
Craig-Schmidt MC, Weete JD, Faircloth SA, Wickwire MA, Livant EJ: The effect of hydrogenated fat in the diet of nursing mothers on lipid composition and prostaglandin content of human milk. Am J Clin Nutr 1984;39: 778–786.
Crawford MA, Hassam AG, Williams G: Essential fatty acids and fetal brain growth. Lancet 1976;1:452–453.
Cunnane SC, Anderson MJ: Pure linoleate deficiency in the rat: influence on growth, accumulation of n–6 polyunsaturates, and [1–14C]linoleate oxidation. J Lipid Res 1997;38: 805–812.
Cunnane SC, Francescutti V, Brenna JT, Crawford MA: Breast-fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahexaenoate. Lipids 2000;35:105–111.
Cunnane SC, Ryan MA, Craig KS, Brookes S, Koletzko B, Demmelmair H, Singer J, Kyle DJ: Synthesis of linoleate and alpha-linolenate by chain elongation in the rat. Lipids 1995;30:781–783.
D'Almeida A, Carter JP, Anatol A, Prost C: Effects of a combination of evening primrose oil (gamma linolenic acid) and fish oil (eicosapentaenoic + docahexaenoic acid) versus magnesium, and versus placebo in preventing pre-eclampsia. Women Health 1992;19: 117–131.
De Vriese SR, Christophe AB, Maes M: Lowered serum n–3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n–PUFAs are related to major depression. Life Sci 2003;73:3181–3187.
De Vriese SR, De Henauw S, De Backer G, Dhont M, Christophe AB: Estimation of dietary fat intake of Belgian pregnant women: comparison of two methods. Ann Nutr Metab 2001; 45:273–278.
Denomme J, Stark KD, Holub BJ: Directly quantitated dietary (n–3) fatty acid intakes of pregnant Canadian women are lower than current dietary recommendations. J Nutr 2005;135:206–211.
Diau GY, Hsieh AT, Sarkadi-Nagy EA, Wijendran V, Nathanielsz PW, Brenna JT: The influence of long chain polyunsaturate supplementation on docosahexaenoic acid and arachidonic acid in baboon neonate central nervous system. BMC Med 2005;3:11.
Diau GY, Loew ER, Wijendran V, Sarkadi-Nagy E, Nathanielsz PW, Brenna JT: Docosahexaenoic and arachidonic acid influence on preterm baboon retinal composition and function. Invest Ophthalmol Vis Sci 2003;44: 4559–4566.
Dobbing J, Sands J: Comparative aspects of the brain growth spurt. Early Hum Dev 1979;3: 79–83.
Dunstan JA, Mitoulas LR, Dixon G, Doherty DA, Hartmann PE, Simmer K, Prescott SL: The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: a randomized, controlled trial. Pediatr Res 2007;62:689–694.
Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL: Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. J Allergy Clin Immunol 2003a;112:1178–1184.
Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL: Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. Clin Exp Allergy 2003b;33:442–448.
Dunstan JA, Simmer K, Dixon G, Prescott SL: Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F45–F50.
Extier A, Langelier B, Perruchot MH, Guesnet P, Van Veldhoven PP, Lavialle M, Alessandri JM: Gender affects liver desaturase expression in a rat model of n–3 fatty acid repletion. J Nutr Biochem 2009. E-pub ahead of print.
Ezaki O, Takahashi M, Shigematsu T, Shimamura K, Kimura J, Ezaki H, Gotoh T: Long-term effects of dietary alpha-linolenic acid from perilla oil on serum fatty acids composition and on the risk factors of coronary heart disease in Japanese elderly subjects. J Nutr Sci Vitaminol (Tokyo) 1999;45:759–772.
Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW: Infant cerebral cortex phospholipid fatty-acid composition and diet. Lancet 1992;340:810–813.
Ferretti A, Nelson GJ, Schmidt PC, Kelley DS, Bartolini G, Flanagan VP: Increased dietary arachidonic acid enhances the synthesis of vasoactive eicosanoids in humans. Lipids 1997;32:435–439.
Fontani G, Corradeschi F, Felici A, Alfatti F, Bugarini R, Fiaschi AI, Cerretani D, Montorfano G, Rizzo AM, Berra B: Blood profiles, body fat and mood state in healthy subjects on different diets supplemented with omega-3 polyunsaturated fatty acids. Eur J Clin Invest 2005;35:499–507.
Foreman-van Drongelen MM, van Houwelingen AC, Kester AD, Hasaart TH, Blanco CE, Hornstra G: Long-chain polyunsaturated fatty acids in preterm infants: status at birth and its influence on postnatal levels. J Pediatr 1995;126:611–618.

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Francois CA, Connor SL, Bolewicz LC, Connor WE: Supplementing lactating women with flaxseed oil does not increase docosahexaenoic acid in their milk. Am J Clin Nutr 2003; 77:226–233.

Frangou S, Lewis M, McCrone P: Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry 2006;188:46–50.

Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ: Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. J Affect Disord 2008;110:142–148.

Freeman MP, Hibbeln JR, Wisner KL, Brumbach BH, Watchman M, Gelenberg AJ: Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. Acta Psychiatr Scand 2006a;113:31–35.

Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet D, Keck PE Jr, Marangell LB, Richardson AJ, Lake J, Stoll AL: Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J Clin Psychiatry 2006b;67:1954–1967.

Freeman MP, Hibbeln JR, Wisner KL, Watchman M, Gelenberg AJ: An open trial of omega-3 fatty acids for depression in pregnancy. Acta Neuropsychiatr 2006c;18:21–24.

Gawrisch K, Soubias O: Structure and dynamics of polyunsaturated hydrocarbon chains in lipid bilayers-significance for GPCR function. Chem Phys Lipids 2008;153:64–75.

Geppert J, Demmelmair H, Hornstra G, Koletzko B: Co-supplementation of healthy women with fish oil and evening primrose oil increases plasma docosahexaenoic acid, gamma-linolenic acid and dihomo-gamma-linolenic acid levels without reducing arachidonic acid concentrations. Br J Nutr 2008;99: 360–369.

Ghafoorunissa SA: Fats in Indian diets and their nutritional and health implications. Lipids 1996;31(suppl):S287–S291.

Ghafoorunissa SA: Requirements of dietary fats to meet nutritional needs and prevent the risk of atherosclerosis – an Indian perspective. Indian J Med Res 1998;108:191–202.

Ghafoorunissa SA: Dietary Fat and Diet-Related Chronic Diseases: Indian Perspective. In Touch. (Heinz Nutrition Foundation India) 2005;7:2–6.

Ghafoorunissa SA, Vani A, Laxmi R, Sesikeran B: Effects of dietary alpha-linolenic acid from blended oils on biochemical indices of coronary heart disease in Indians. Lipids 2002;37:1077–1086.

Gibson RA, Neumann MA, Makrides M: Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. Eur J Clin Nutr 1997;51: 578–584.

Giltay EJ, Duschek EJ, Katan MB, Zock PL, Neele SJ, Netelenbos JC: Raloxifene and hormone replacement therapy increase arachidonic acid and docosahexaenoic acid levels in postmenopausal women. J Endocrinol 2004a;182: 399–408.

Giltay EJ, Gooren LJ, Toorians AW, Katan MB, Zock PL: Docosahexaenoic acid concentrations are higher in women than in men because of estrogenic effects. Am J Clin Nutr 2004b;80:1167–1174.

Greiner RC, Winter J, Nathanielsz PW, Brenna JT: Brain docosahexaenoate accretion in fetal baboons: bioequivalence of dietary alpha-linolenic and docosahexaenoic acids. Pediatr Res 1997;42:826–834.

Guesnet P, Pugo-Gunsam P, Maurage C, Pinault M, Giraudeau B, Alessandri JM, Durand G, Antoine JM, Couet C: Blood lipid concentrations of docosahexaenoic and arachidonic acids at birth determine their relative postnatal changes in term infants fed breast milk or formula. Am J Clin Nutr 1999;70:292–298.

Gura KM, Duggan CP, Collier SB, Jennings RW, Folkman J, Bistrian BR, Puder M: Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:e197–e201.

Gura KM, Lee S, Valim C, Zhou J, Kim S, Modi BP, Arsenault DA, Strijbosch RA, Lopes S, Duggan C, Puder M: Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678–e686.

Hadders-Algra M: Prenatal docosahexaenoic acid (DHA) and arachidonic acid (AA) supplementation better for neurodevelopment than supplementation with DHA only? J Perinat Med 2008a;36:268–269.

Hadders-Algra M: Prenatal long-chain polyunsaturated fatty acid status: the importance of a balanced intake of docosahexaenoic acid and arachidonic acid. J Perinat Med 2008b; 36:101–109.

Haggarty P, Ashton J, Joynson M, Abramovich DR, Page K: Effect of maternal polyunsaturated fatty acid concentration on transport by the human placenta. Biol Neonate 1999; 75:350–359.

Hallahan B, Hibbeln JR, Davis JM, Garland MR: Omega-3 fatty acid supplementation in patients with recurrent self-harm: single-centre double-blind randomised controlled trial. Br J Psychiatry 2007;190:118–122.

Harris WS, Lemke SL, Hansen SN, Goldstein DA, Dirienzo MA, Su H, Nemeth MA, Taylor ML, Ahmed G, George C: Stearidonic acid-enriched soybean oil increased the omega-3 index, an emerging cardiovascular risk marker. Lipids 2008;43:805–811.

Haubner LY, Stockard JE, Saste MD, Benford VJ, Phelps CP, Chen LT, Barness L, Wiener D, Carver JD: Maternal dietary docosahexanoic acid content affects the rat pup auditory system. Brain Res Bull 2002;58:1–5.

Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T, Drevon CA: Similar effects on infants of n–3 and n–6 fatty acids supplementation to pregnant and lactating women. Pediatrics 2001;108:E82.

Helland IB, Smith L, Blomen B, Saarem K, Saugstad OD, Drevon CA: Effect of supplementing pregnant and lactating mothers with n–3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. Pediatrics 2008;122:e472–e479.

Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA: Maternal supplementation with very-long-chain n–3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 2003;111:e39–e44.

Hibbeln JR: Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J Affect Disord 2002;69:15–29.

Hibbeln JR, Davis JM: Considerations regarding putative daily reference intakes (DRI's) for omega-3 long chain fatty acids. Am J Clin Nutr 2009. In submission.

Hibbeln JR, Davis JM, Steer C, Emmett P, Golding J: Authors' reply. Lancet 2007a;370:219–220.

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J: Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 2007b;369:578–585.

Holman RT: The slow discovery of the importance of omega 3 essential fatty acids in human health. J Nutr 1998;128(suppl):427S–433S.

Hornstra G: Essential fatty acids in mothers and their neonates. Am J Clin Nutr 2000;71 (suppl):1262S–1269S.

Hornstra G, van Eijsden M, Dirix C, Bonsel G: *Trans* fatty acids and birth outcome: some first results of the MEFAB and ABCD cohorts. Atheroscler Suppl 2006;7:21–23.

Horvath A, Koletzko B, Szajewska H: Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Br J Nutr 2007; 98:253–259.

Hsieh AT, Anthony JC, Diersen-Schade DA, Rumsey SC, Lawrence P, Li C, Nathanielsz PW, Brenna JT: The influence of moderate and high dietary long chain polyunsaturated fatty acids (LCPUFA) on baboon neonate tissue fatty acids. Pediatr Res 2007;61(part 1):537–545.

Innis SM, Elias SL: Intakes of essential n–6 and n–3 polyunsaturated fatty acids among pregnant Canadian women. Am J Clin Nutr 2003; 77:473–478.

Innis SM, Friesen RW: Essential n–3 fatty acids in pregnant women and early visual acuity maturation in term infants. Am J Clin Nutr 2008;87:548–557.

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54.81.83.207 - 6/24/2017 11:00:54 PM

Innis SM, King DJ: *Trans* fatty acids in human milk are inversely associated with concentrations of essential all-*cis* n–6 and n–3 fatty acids and determine *trans*, but not n–6 and n–3, fatty acids in plasma lipids of breast-fed infants. Am J Clin Nutr 1999;70:383–390.

James MJ, Ursin VM, Cleland LG: Metabolism of stearidonic acid in human subjects: comparison with the metabolism of other n–3 fatty acids. Am J Clin Nutr 2003;77:1140–1145.

Jensen CL, Chen H, Fraley JK, Anderson RE, Heird WC: Biochemical effects of dietary linoleic/alpha-linolenic acid ratio in term infants. Lipids 1996;31:107–113.

Jensen CL, Voigt RG, Prager TC, Zou YL, Fraley JK, Rozelle JC, Turcich MR, Llorente AM, Anderson RE, Heird WC: Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. Am J Clin Nutr 2005;82:125–132.

Jensen RG, Hagerty MM, McMahon KE: Lipids of human milk and infant formulas: a review. Am J Clin Nutr 1978;31:990–1016.

Jensen RG, Lammi-Keefe CJ, Henderson RA, Bush VJ, Ferris AM: Effect of dietary intake of n–6 and n–3 fatty acids on the fatty acid composition of human milk in North America. J Pediatr 1992;120(part 2):S87–S92.

Judge MP, Harel O, Lammi-Keefe CJ: A docosahexaenoic acid-functional food during pregnancy benefits infant visual acuity at four but not six months of age. Lipids 2007a;42:117–122.

Judge MP, Harel O, Lammi-Keefe CJ: Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. Am J Clin Nutr 2007b;85:1572–1577.

Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS, Denicoff KD, Grunze H, Duan N, Post RM: Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. Biol Psychiatry 2006;60:1020–1022.

Kelley DS, Taylor PC, Nelson GJ, Schmidt PC, Mackey BE, Kyle D: Effects of dietary arachidonic acid on human immune response. Lipids 1997;32:449–456.

Kent JC, Mitoulas LR, Cregan MD, Ramsay DT, Doherty DA, Hartmann PE: Volume and frequency of breastfeedings and fat content of breast milk throughout the day. Pediatrics 2006;117:e387–e395.

Khan AH, Carson RJ, Nelson SM: Prostaglandins in labor – a translational approach. Front Biosci 2008;13:5794–5809.

Klingler M, Demmelmair H, Larqué E, Koletzko B: Analysis of FA contents in individual lipid fractions from human placental tissue. Lipids 2003;38:561–566.

Koletzko B: Prenatal supply of docosahexaenoic acid (DHA): should we be worried? J Perinat Med 2008;36:265–267, author reply 268–269.

Koletzko B, Cetin I, Brenna JT: Dietary fat intakes for pregnant and lactating women. Br J Nutr 2007;98:873–877.

Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, Willatts P, Uauy R: The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. J Perinat Med 2008;36:5–14.

Koletzko B, Müller J: *Cis*- and *trans*-isomeric fatty acids in plasma lipids of newborn infants and their mothers. Biol Neonate 1990;57:172–178.

Krauss-Etschmann S, Hartl D, Rzehak P, Heinrich J, Shadid R, Del Carmen Ramirez-Tortosa M, Campoy C, Pardillo S, Schendel DJ, Decsi T, Demmelmair H, Koletzko BV: Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. J Allergy Clin Immunol 2008;121:464–470, e466.

Krauss-Etschmann S, Shadid R, Campoy C, Hoster E, Demmelmair H, Jimenez M, Gil A, Rivero M, Veszpremi B, Decsi T, Koletzko BV: Effects of fish-oil and folate supplementation of pregnant women on maternal and fetal plasma concentrations of docosahexaenoic acid and eicosapentaenoic acid: a European randomized multicenter trial. Am J Clin Nutr 2007;85:1392–1400.

Lakin V, Haggarty P, Abramovich DR, Ashton J, Moffat CF, McNeill G, Danielian PJ, Grubb D: Dietary intake and tissue concentration of fatty acids in omnivore, vegetarian and diabetic pregnancy. Prostaglandins Leukot Essent Fatty Acids 1998;59:209–220.

Lamptey MS, Walker BL: Learning behavior and brain lipid composition in rats subjected to essential fatty acid deficiency during gestation, lactation and growth. J Nutr 1978;108:358–367.

Lapillonne A, Jensen CL: Reevaluation of the DHA requirement for the premature infant Am J Clin Nutr 2009. E-pub ahead of print.

Larnkjaer A, Christensen JH, Michaelsen KF, Lauritzen L: Maternal fish oil supplementation during lactation does not affect blood pressure, pulse wave velocity, or heart rate variability in 2.5-y-old children. J Nutr 2006;136:1539–1544.

Larqué E, Demmelmair H, Berger B, Hasbargen U, Koletzko B: In vivo investigation of the placental transfer of (13)C-labeled fatty acids in humans. J Lipid Res 2003;44:49–55.

Lauritzen L, Hoppe C, Straarup EM, Michaelsen KF: Maternal fish oil supplementation in lactation and growth during the first 2.5 years of life. Pediatr Res 2005a;58:235–242.

Lauritzen L, Jorgensen MH, Mikkelsen TB, Skovgaard M, Straarup EM, Olsen SF, Hoy CE, Michaelsen KF: Maternal fish oil supplementation in lactation: effect on visual acuity and n–3 fatty acid content of infant erythrocytes. Lipids 2004;39:195–206.

Lauritzen L, Jorgensen MH, Olsen SF, Straarup EM, Michaelsen KF: Maternal fish oil supplementation in lactation: effect on developmental outcome in breast-fed infants. Reprod Nutr Dev 2005b;45:535–547.

Lauritzen L, Kjaer TM, Fruekilde MB, Michaelsen KF, Frokiaer H: Fish oil supplementation of lactating mothers affects cytokine production in 2 1/2-year-old children. Lipids 2005c;40:669–676.

Lewin GA, Schachter HM, Yuen D, Merchant P, Mamaladze V, Tsertsvadze A, Clifford T, Kourad K, Barnes D, Armour T, Yazdi F, MacNeil J, McGahern C, Senechal C, Fang M, Barrowman N, Sampson M, Morrison A, Elien D, Saint-Martin M, Sambasivan A, Lowcock E, Pan Y, Lemyre B: Effects of omega-3 fatty acids on child and maternal health. Evid Rep Technol Assess (Summ) 2005;118:1–11.

Lewis NM, Widga AC, Buck JS, Frederick AM: Survey of omega-3 fatty acids in diets of Midwest low-income pregnant women. J Agromed 1995;2:49–57.

Lin PY, Su KP: A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry 2007;68:1056–1061.

Loosemore ED, Judge MP, Lammi-Keefe CJ: Dietary intake of essential and long-chain polyunsaturated fatty acids in pregnancy. Lipids 2004;39:421–424.

Mahomed K, Williams MA, King IB, Mudzamiri S, Woelk GB: Erythrocyte omega-3, omega-6 and trans fatty acids in relation to risk of preeclampsia among women delivering at Harare Maternity Hospital, Zimbabwe. Physiol Res 2007;56:37–50.

Makrides M, Duley L, Olsen SF: Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. Cochrane Database Syst Rev 2006;3:CD003402.

Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA: Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189–194.

Malcolm CA, Hamilton R, McCulloch DL, Montgomery C, Weaver LT: Scotopic electroretinogram in term infants born of mothers supplemented with docosahexaenoic acid during pregnancy. Invest Ophthalmol Vis Sci 2003a;44:3685–3691.

Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT: Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. Arch Dis Child Fetal Neonatal Ed 2003b;88:F383–F390.

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54.81.83.207 - 6/24/2017 11:00:54 PM

Malerba G, Schaeffer L, Xumerle L, Klopp N, Trabetti E, Biscuola M, Cavallari U, Galavotti R, Martinelli N, Guarini P, Girelli D, Olivieri O, Corrocher R, Heinrich J, Pignatti PF, Illig T: SNPs of the FADS gene cluster are associated with polyunsaturated fatty acids in a cohort of patients with cardiovascular disease. Lipids 2008;43:289–299.

Mantzioris E, James MJ, Gibson RA, Cleland LG: Dietary substitution with an alpha-linolenic acid-rich vegetable oil increases eicosapentaenoic acid concentrations in tissues. Am J Clin Nutr 1994;59:1304–1309.

Mantzioris E, James MJ, Gibson RA, Cleland LG: Differences exist in the relationships between dietary linoleic and alpha-linolenic acids and their respective long-chain metabolites. Am J Clin Nutr 1995;61:320–324.

Marangell LB, Martinez JM, Zboyan HA, Chong H, Puryear LJ: Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. Depress Anxiety 2004;19:20–23.

Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ: A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. Am J Psychiatry 2003; 160:996–998.

Martinez M: Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr 1992;120(part 2):S129–S138.

McNamara RK, Hahn CG, Jandacek R, Rider T, Tso P, Stanford KE, Richtand NM: Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. Biol Psychiatry 2007;62: 17–24.

Messeri GP, Oliverio A, Paoletti R, Galli C: Deficiency of essential fatty acids during pregnancy and avoidance learning in the progeny. Pharmacol Res Commun 1975;7:71–80.

Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu SL, Papakostas GI, Dording CM, Sonawalla SB, Nierenberg AA, Alpert JE, Fava M: A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. Eur Neuropsychopharmacol 2008;18:639–645.

Mitoulas LR, Gurrin LC, Doherty DA, Sherriff JL, Hartmann PE: Infant intake of fatty acids from human milk over the first year of lactation. Br J Nutr 2003;90:979–986.

Molteni RA: Placental growth and fetal/placental weight (F/P) ratios throughout gestation – their relationship to patterns of fetal growth. Semin Perinatol 1984;8:94–100.

Montgomery C, Speake BK, Cameron A, Sattar N, Weaver LT: Maternal docosahexaenoic acid supplementation and fetal accretion. Br J Nutr 2003;90:135–145.

Moodley J, Norman RJ: Attempts at dietary alteration of prostaglandin pathways in the management of pre-eclampsia. Prostaglandins Leukot Essent Fatty Acids 1989;37:145–147.

Morrison JA, Glueck CJ, Wang P: Dietary trans fatty acid intake is associated with increased fetal loss. Fertil Steril 2008;90:385–390.

Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B, Wisner KL: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA 2005; 293:2372–2383.

Mott GE, Jackson EM, McMahan CA, McGill HC Jr: Cholesterol metabolism in adult baboons is influenced by infant diet. J Nutr 1990;120:243–251.

Nelson GJ, Kelley DS, Emken EA, Phinney SD, Kyle D, Ferretti A: A human dietary arachidonic acid supplementation study conducted in a metabolic research unit: rationale and design. Lipids 1997a;32:415–420.

Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Kyle D: The effect of dietary arachidonic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. Lipids 1997b;32:421–425.

Nelson GJ, Schmidt PC, Bartolini G, Kelley DS, Phinney SD, Kyle D, Silbermann S, Schaefer EJ: The effect of dietary arachidonic acid on plasma lipoprotein distributions, apoproteins, blood lipid levels, and tissue fatty acid composition in humans. Lipids 1997c;32: 427–433.

Nemets B, Stahl Z, Belmaker RH: Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159: 477–479.

Nesheim MC, Yaktine AL: Seafood Choices: Balancing Benefits and Risks. Washington, Institute of Medicine of the National Academies, 2007, p 465.

Neuringer M, Connor WE, Lin DS, Barstad L, Luck S: Biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys. Proc Natl Acad Sci USA 1986;83:4021–4025.

Oken E, Ning Y, Rifas-Shiman SL, Rich-Edwards JW, Olsen SF, Gillman MW: Diet during pregnancy and risk of preeclampsia or gestational hypertension. Ann Epidemiol 2007;17:663–668.

Oken E, Osterdal ML, Gillman MW, Knudsen VK, Halldorsson TI, Strom M, Bellinger DC, Hadders-Algra M, Michaelsen KF, Olsen SF: Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. Am J Clin Nutr 2008; 88:789–796.

Olsen SF, Osterdal ML, Salvig JD, Mortensen LM, Rytter D, Secher NJ, Henriksen TB: Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. Am J Clin Nutr 2008;88:167–175.

Olsen SF, Osterdal ML, Salvig JD, Weber T, Tabor A, Secher NJ: Duration of pregnancy in relation to fish oil supplementation and habitual fish intake: a randomised clinical trial with fish oil. Eur J Clin Nutr 2007;61:976–985.

Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Gluud C: Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team. BJOG 2000;107:382–395.

Olsen SF, Sorensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A: Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. Lancet 1992;339:1003–1007.

Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D: A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. Br J Obstet Gynaecol 1995;102: 95–100.

Otto SJ, van Houwelingen AC, Badart-Smook A, Hornstra G: Changes in the maternal essential fatty acid profile during early pregnancy and the relation of the profile to diet. Am J Clin Nutr 2001;73:302–307.

Otto SJ, van Houwelingen AC, Hornstra G: The effect of supplementation with docosahexaenoic and arachidonic acid derived from single cell oils on plasma and erythrocyte fatty acids of pregnant women in the second trimester. Prostaglandins Leukot Essent Fatty Acids 2000;63:323–328.

Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG: Infant feeding and blood cholesterol: a study in adolescents and a systematic review. Pediatrics 2002;110:597–608.

Park WJ, Kothapalli KS, Lawrence P, Tyburczy C, Brenna JT: An alternate pathway to long-chain polyunsaturates: the FADS2 gene product Δ8-desaturates 20:2n–6 and 20: 3n–3. J Lipid Res 2009;50:1195–1202.

Parra MS, Schnaas L, Meydani M, Perroni E, Martínez S, Romieu I: Erythrocyte cell membrane phospholipid levels compared against reported dietary intakes of polyunsaturated fatty acids in pregnant Mexican women. Public Health Nutr 2002;5:931–937.

Pawlosky RJ, Hibbeln JR, Salem N Jr: Compartmental analyses of plasma n–3 essential fatty acids among male and female smokers and nonsmokers. J Lipid Res 2007;48:935–943.

Pawlosky RJ, Lin YH, Llanos A, Mena P, Uauy R, Salem N Jr: Compartmental analyses of plasma 13C- and 2H-labeled n–6 fatty acids arising from oral administrations of 13C-U-18: 2n–6 and 2H5-20:3n–6 in newborn infants. Pediatr Res 2006;60:327–333.

Peet M, Horrobin DF: A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. J Psychiatr Res 2002;36:7–18.

Pisani LP, Oller do Nascimento CM, Bueno AA, Biz C, Albuquerque KT, Ribeiro EB, Oyama LM: Hydrogenated fat diet intake during pregnancy and lactation modifies the PAI-1 gene expression in white adipose tissue of offspring in adult life. Lipids Health Dis 2008a;7:13.

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Pisani LP, Oyama LM, Bueno AA, Biz C, Albuquerque KT, Ribeiro EB, Oller do Nascimento CM: Hydrogenated fat intake during pregnancy and lactation modifies serum lipid profile and adipokine mRNA in 21-day-old rats. Nutrition 2008b;24:255–261.

Plourde M, Cunnane SC: Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. Appl Physiol Nutr Metab 2007;32:619–634, see also erratum: Appl Physiol Nutr Metab 633:228 (2008).

Ponnampalam EN, Mann NJ, Sinclair AJ: Effect of feeding systems on omega-3 fatty acids, conjugated linoleic acid and trans fatty acids in Australian beef cuts: potential impact on human health. Asia Pac J Clin Nutr 2006;15: 21–29.

Prescott SL, Barden AE, Mori TA, Dunstan JA: Maternal fish oil supplementation in pregnancy modifies neonatal leukotriene production by cord-blood-derived neutrophils. Clin Sci (Lond) 2007;113:409–416.

Puder M; (personal communication) 2008.

Radesky JS, Oken E, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Gillman MW: Diet during early pregnancy and development of gestational diabetes. Paediatr Perinat Epidemiol 2008;22:47–59.

Raeder MB, Steen VM, Vollset SE, Bjelland I: Associations between cod liver oil use and symptoms of depression: the Hordaland Health Study. J Affect Disord 2007;101:245–249.

Rees AM, Austin MP, Parker GB: Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. Aust NZ J Psychiatry 2008; 42:199–205.

Reiser R, Sidelman Z: Control of serum cholesterol homeostasis by cholesterol in the milk of the suckling rat. J Nutr 1972;102:1009–1016.

Richardson AJ: n–3 Fatty acids and mood: the devil is in the detail. Br J Nutr 2008;99:221–223.

Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, Heatherley SV, Christian LM, McNaughton SA, Ness AR: No effect of n–3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. Br J Nutr 2008;99:421–431.

Ruyle M, Connor WE, Anderson GJ, Lowensohn RI: Placental transfer of essential fatty acids in humans: venous-arterial difference for docosahexaenoic acid in fetal umbilical erythrocytes. Proc Natl Acad Sci USA 1990; 87:7902–7906.

Rzehak P, Heinrich J, Klopp N, Schaeffer L, Hoff S, Wolfram G, Illig T, Linseisen J: Evidence for an association between genetic variants of the fatty acid desaturase 1 fatty acid desaturase 2 (FADS1 FADS2) gene cluster and the fatty acid composition of erythrocyte membranes. Br J Nutr 2009;101:20–26.

Saldana TM, Siega-Riz AM, Adair LS: Effect of macronutrient intake on the development of glucose intolerance during pregnancy. Am J Clin Nutr 2004;79:479–486.

Salem N Jr, Moriguchi T, Greiner RS, McBride K, Ahmad A, Catalan JN, Slotnick B: Alterations in brain function after loss of docosahexaenoate due to dietary restriction of n–3 fatty acids. J Mol Neurosci 2001;16:299–307, discussion 317–221.

Sanders TA, Reddy S: The influence of a vegetarian diet on the fatty acid composition of human milk and the essential fatty acid status of the infant. J Pediatr 1992;120(part 2):S71–S77.

Sanjurjo P, Ruiz-Sanz JI, Jimeno P, Aldámiz-Echevarría L, Aquino L, Matorras R, Esteban J, Banqué M: Supplementation with docosahexaenoic acid in the last trimester of pregnancy: maternal-fetal biochemical findings. J Perinat Med 2004;32:132–136.

Sarkadi-Nagy E, Wijendran V, Diau GY, Chao AC, Hsieh AT, Turpeinen A, Nathanielsz PW, Brenna JT: The influence of prematurity and long chain polyunsaturate supplementation in 4-week adjusted age baboon neonate brain and related tissues. Pediatr Res 2003; 54:244–252.

Saste MD, Carver JD, Stockard JE, Benford VJ, Chen LT, Phelps CP: Maternal diet fatty acid composition affects neurodevelopment in rat pups. J Nutr 1998;128:740–743.

Schack-Nielsen L, Michaelsen KF: Breast feeding and future health. Curr Opin Clin Nutr Metab Care 2006;9:289–296.

Schaeffer L, Gohlke H, Müller M, Heid IM, Palmer LJ, Kompauer I, Demmelmair H, Illig T, Koletzko B, Heinrich J: Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 2006;15: 1745–1756.

Seyberth HW, Oelz O, Kennedy T, Sweetman BJ, Danon A, Frölich JC, Heimberg M, Oates JA: Increased arachidonate in lipids after administration to man: effects on prostaglandin biosynthesis. Clin Pharmacol Ther 1975; 18(5 Pt 1):521–529.

Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA: Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. Prostaglandins Leukot Essent Fatty Acids 2005;72:211–218.

Sinclair AJ, Mann NJ: Short-term diets rich in arachidonic acid influence plasma phospholipid polyunsaturated fatty acid levels and prostacyclin and thromboxane production in humans. J Nutr 1996;126(suppl 4):1110S–1114S.

Sinclair AJ, O'Dea K, Naughton JM: Elevated levels of arachidonic acid in fish from northern Australian waters. Lipids 1983;18:877–881.

Smit LA, Mozaffarian D, Willett W: Review of fat and fatty acid requirements and criteria for developing dietary guidelines. Ann Nutr Metab 2009;55:44–55.

Smuts CM, Borod E, Peeples JM, Carlson SE: High-DHA eggs: feasibility as a means to enhance circulating DHA in mother and infant. Lipids 2003a;38:407–414.

Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE: A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol 2003b;101:469–479.

Sontrop J, Campbell MK: Omega-3 polyunsaturated fatty acids and depression: a review of the evidence and a methodological critique. Prev Med 2006;42:4–13.

Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB: Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56:407–412.

Su HM, Bernardo L, Mirmiran M, Ma XH, Corso TN, Nathanielsz PW, Brenna JT: Bioequivalence of dietary alpha-linolenic and docosahexaenoic acids as sources of docosahexaenoate accretion in brain and associated organs of neonatal baboons. Pediatr Res 1999;45:87–93.

Su HM, Brenna JT: Simultaneous measurement of desaturase activities using stable isotope tracers or a nontracer method. Anal Biochem 1998;261:43–50.

Su KP, Huang SY, Chiu CC, Shen WW: Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol 2003;13:267–271.

Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, Pariante CM: Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2008;69:644–651.

Szajewska H, Horvath A, Koletzko B: Effect of n–3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2006;83:1337–1344.

Tanaka K, Kon N, Ohkawa N, Yoshikawa N, Shimizu T: Does breastfeeding in the neonatal period influence the cognitive function of very-low-birth-weight infants at 5 years of age? Brain Dev 2009;31:288–293.

Thies F, Miles EA, Nebe-von-Caron G, Powell JR, Hurst TL, Newsholme EA, Calder PC: Influence of dietary supplementation with long-chain n–3 or n–6 polyunsaturated fatty acids on blood inflammatory cell populations and functions and on plasma soluble adhesion molecules in healthy adults. Lipids 2001a;36:1183–1193.

Thies F, Nebe-von-Caron G, Powell JR, Yaqoob P, Newsholme EA, Calder PC: Dietary supplementation with eicosapentaenoic acid, but not with other long-chain n–3 or n–6 polyunsaturated fatty acids, decreases natural killer cell activity in healthy subjects aged >55 y. Am J Clin Nutr 2001b;73:539–548.

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Thies F, Nebe-von-Caron G, Powell JR, Yaqoob P, Newsholme EA, Calder PC: Dietary supplementation with gamma-linolenic acid or fish oil decreases T lymphocyte proliferation in healthy older humans. J Nutr 2001c;131: 1918–1927.

Thomas B, Ghebremeskel K, Lowy C, Crawford M, Offley-Shore B: Nutrient intake of women with and without gestational diabetes with a specific focus on fatty acids. Nutrition 2006;22:230–236.

Tofail F, Kabir I, Hamadani JD, Chowdhury F, Yesmin S, Mehreen F, Huda SN: Supplementation of fish-oil and soy-oil during pregnancy and psychomotor development of infants. J Health Popul Nutr 2006;24:48–56.

Tyburczy C, Major C, Lock AL, Destaillats F, Mouloungui Z, Candy L, Lawrence P, Brenna JT, Salter AM, Bauman DE: Individual *trans* octadecenoic acids and partially hydrogenated vegetable oil differentially affect hepatic lipid and lipoprotein metabolism in golden Syrian hamsters. J Nutr 2009;139: 257–263.

Uauy R, Mena P, Wegher B, Nieto S, Salem N Jr: Long chain polyunsaturated fatty acid formation in neonates: effect of gestational age and intrauterine growth. Pediatr Res 2000; 47:127–135.

van Eijsden M, Hornstra G, van der Wal MF, Vrijkotte TG, Bonsel GJ: Maternal n–3, n–6, and *trans* fatty acid profile early in pregnancy and term birth weight: a prospective cohort study. Am J Clin Nutr 2008;87:887–895.

van Houwelingen AC, Sorensen JD, Hornstra G, Simonis MM, Boris J, Olsen SF, Secher NJ: Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. Br J Nutr 1995;74:723–731.

Wainwright PE, Xing HC, Mutsaers L, McCutcheon D, Kyle D: Arachidonic acid offsets the effects on mouse brain and behavior of a diet with a low (n–6):(n–3) ratio and very high levels of docosahexaenoic acid. J Nutr 1997;127:184–193.

Wang Y, Storlien LH, Jenkins AB, Tapsell LC, Jin Y, Pan JF, Shao YF, Calvert GD, Moses RG, Shi HL, Zhu XX: Dietary variables and glucose tolerance in pregnancy. Diabetes Care 2000;23:460–464.

Weaver KL, Ivester P, Chilton JA, Wilson MD, Pandey P, Chilton FH: The content of favorable and unfavorable polyunsaturated fatty acids found in commonly eaten fish. J Am Diet Assoc 2008;108:1178–1185.

Wijendran V, Bendel RB, Couch SC, Philipson EH, Thomsen K, Zhang X, Lammi-Keefe CJ: Maternal plasma phospholipid polyunsaturated fatty acids in pregnancy with and without gestational diabetes mellitus: relations with maternal factors. Am J Clin Nutr 1999; 70:53–61.

Williams C, Birch EE, Emmett PM, Northstone K: Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. Am J Clin Nutr 2001;73:316–322.

Williams MA, King IB, Sorensen TK, Zingheim RW, Troyer BL, Zebelman AM, Luthy DA: Risk of preeclampsia in relation to elaidic acid (*trans* fatty acid) in maternal erythrocytes. Gynecol Obstet Invest 1998;46:84–87.

Xie L, Innis SM: Genetic variants of the FADS1 FADS2 gene cluster are associated with altered (n–6) and (n–3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr 2008;138:2222–2228.

Yuhas R, Pramuk K, Lien EL: Human milk fatty acid composition from nine countries varies most in DHA. Lipids 2006;41:851–858.

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